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Prevalence of Preeclampsia Causing Pregnancy Complications and Its Associated Risk Factors Among Women in Rajshahi Region

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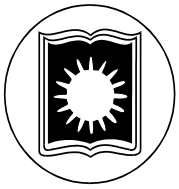
PREVALENCE OF PREECLAMPSIA CAUSING PREGNANCY COMPLICATIONS AND ITS ASSOCIATED RISK FACTORS AMONG WOMEN IN RAJSHAHI REGION



THESIS SUBMITTED FOR THE DEGREE
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BY

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NOVEMBER, 2020

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Dedicated

To

My Beloved Parents

DECLARATION

I do hereby declare that the entire research work, entitled "*Prevalence of Preeclampsia Causing Pregnancy Complications And Its Associated Risk Factors Among Women in Rajshahi Region*" in Institute of Biological Sciences, as embodied in this dissertation towards the fulfillment of Ph. D. degree is the result of my own investigation except where due acknowledgement has been given.

I further declare that all Ethical Guidelines were followed properly and that the thesis or part of it has not concurrently been submitted elsewhere for any other degree or diploma.

SULTANA NASIMA AKHTER

CERTIFICATE

This is to certify that SULTANA NASIMA AKHTER is the author of the thesis entitled "*Prevalence Of Preeclampsia Causing Pregnancy Complications And Its Associated Risk Factors Among Women In Rajshahi Region*" submitted to the Institute of Biological Sciences, University of Rajshahi, Bangladesh for the degree of Doctor of Philosophy. She worked under our supervision.

To the best of our knowledge, the thesis has not been previously submitted elsewhere for any degree or diploma. We are forwarding this thesis for the examination/evaluation for the degree of Doctor of Philosophy awarded by University of Rajshahi, Bangladesh.

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ABSTRACT

Preeclampsia is an acute multi-system obstetrical disorder that claims the lives of more than 70,000 women and 500,000 of their fetuses and newborns each year. This investigation was a cross-sectional study that was conducted mainly in Rajshahi Medical College Hospital and its vicinity. This study reports the prevalence of preeclampsia as well as some unfocused but potential risk factors such as the effects of environmental pollution (air, water and sound), maternal mental stress, etc. The relationship between concerned gynecological and obstetrical factors and preeclampsia was also reported.

The number of pregnant mothers admitted into Rajshahi Medical College Hospital (RMCH) for delivery or obstructed complications was found to increase from 11,532 to 17,201 during the year 2013 to 2017. Consequently, the number of preeclamptic patients was increased from 407 to 435. The average number of preeclamptic patients found in RMCH per year was 484 (during the last five years). This is equivalent to 3.21% of total pregnant mothers admitted into RMCH for delivery or with obstructed complications. The incidence rate of preeclampsia in pregnant women in Rajshahi region was decreasing with respect to time. With the observed trend, it can be forecasted that in the years 2020, 2023 and 2026 the preeclampsia incidence rate should be 2.02%, 1.30% and 0.58% respectively.

The age of the participating preeclamptic patients ranged from 16 to 40 years, with an average of 25.90 ± 0.65 years. The 69% of the preeclamptic patients were below the age of 29 years. About one-fourth of the preeclamptic mothers were below 20 years, whereas only 1% mother was at 40 years. This reflected that the youngest mothers were at high risk of preeclampsia.

On the basis of BMI values obtained, the preeclamptic patients were classified as Underweight (< 18.5), Normal (18.5–24.9), Overweight (25–29.9) and Obese (≥ 30). It was found that as the patients were more obese, the occurrence of preeclampsia was increased more. The nutritional status of the preeclamptic patients was: Obese (40%) > Overweight (29%) = Normal (29%) > Underweight (2%). The gained weight for the pregnant women at 40 weeks gestation was 11.3 - 15.9 kg for normal, 6.8–11.3 kg for overweight and 5.0–9.1 kg for obese mother. The obese or overweight pregnant preeclamptic mothers were associated with some additional complications including severe edema, severe headache, vomiting, lower abdominal pain and hyperacidity.

The preeclamptic patients' had mainly A+, B+ or O+ blood groups. The prevalence of preeclampsia based on patients' blood grouping was as follows: A+ (39%) > B+ (33%) > O+ (24%) > AB+ (2%) = O– (2%). No preeclamptic patients had A–, B– and AB– blood groups and only 2% patients had very rare O– blood group.

The prevalence of graduate and masters level completed preeclamptic patients was found as 20.00%. The vulnerable preeclamptic patients were under matriculated, which accounted for 66.67%. Thus two-thirds of the patients completed education level 10. The 4.44% preeclamptic patients were also illiterate. This indicates that the preeclamptic patients were not very conscious about preventing preeclampsia.

Socio-economic Index (SEI) is a measure of social class, which was determined from patient's occupation, education, income level and wealth. Out of 90 preeclamptic patients, 69 were within the SEI range of 10–30, whereas 21 were above the range. This reflects that about three-fourths of the concerned patients were of lower social class.

The 89% patients were Muslims and 11% were Hindus. 38 patients (42.22%) were from Single Families, whereas 52 (57.78%) from Joint Families. On the basis of patients' occupation, 80 (88.89%) were housewives, 6 (6.67%) were teachers and 4 (4.44%) were in other services. Regarding ethnicity all were local women, not migrated. Among the pregnant women, 61% were white, 13% were gray and 26% were black. The pregnant women took more protein, vegetables and fruits than average person. But they took less amount of required liquid, which is essential for expanding extra-cellular space and amniotic fluid. The 51.11% of total women took drinking water below the recommended level of 2.2 L/day.

Most of the patients' living rooms were within 15 feet from kitchen. Only 10% patients had good room ventilation, while the remaining 90% patients had either moderate or poor room ventilation. Hence the preeclamptic patients were subjected to moderate CO_2 exposure.

The 78.89% of the preeclamptic patients' living rooms were less than 50 ft from the nearest roads. The value was 84.44% for 100 ft distance. Therefore, it is reasonable that they would experience sound pollution. The sources of intense sound pollution included intense sound of Govt. owned sugar mill, private sugarcane crusher mill, diesel driven power generator, hydraulic horn of some trucks and buses, movement of rail car with whistle, etc. Combination of these two factors revealed that 60% of the preeclamptic patients experienced moderate to intense sound pollution.

Comparison of the groundwater data with WHO guideline values reveals that Arsenic (As), Calcium (Ca), Magnesium (Mg), Iron (Fe) and Sodium (Na) concentrations in the patients' drinking water were comparatively high. The higher values of Ca and Mg indicate that the waters were hard. This along with elevated

level of Fe might favor constipation. Na might assist in developing mild hypertension. The observed high level of arsenic in drinking water (maximum concentration of 164 μg L^{-1}) might facilitate several adverse health effects of acute lethality to chronic effects including vascular diseases, hypertension, cancer, genotoxicity, hyperpigmentation, diabetes mellitus, repeated abortions, stillbirth, preeclampsia, etc. Therefore, safe drinking water is a concern for preeclamptic patients.

The study reveals that 94% of the preeclamptic mothers were under high or very high mental stress, of which 24% were very high and 70% were high. High mental pressure might induce hypertension and hence it is a potential risk factor for preeclampsia.

The preeclamptic patients' first period was in the range of 11-15 years, averaging 12.9 years. Before being pregnant, 85.45% patients' period was regular; whereas only 5.5% irregular. The 58% of the patients became pregnant earlier, of which 20% had their children. In this case, the delivery order was as follows: NDV > C/S > Abortion. After giving birth, 48% of them used steroid contained pills as contraceptive method. The 60% patients had no record of past surgical history. Appendisectomy, DE&C, MR, left Salphingo-oophorectomy and previous C/S occurred for other cases. The principal family history include: Hypertension > Diabetes > Heart disease > Preeclampsia > Cancer.

Among the major complications of the preeclampsia, severe edema alone represented 44%, whereas headache and neck pain 19%, edema and hyperacidity 17%, lower abdominal and chest pain 12%, edema and vomiting 5% and blurring of vision 3%. The patients' blood pressure fluctuated fairly, but remained in higher level. The highest blood pressure was recorded as 210/140 for the patient of 40 weeks gestation. It was generally found that after delivery, the patients' B.P. fell down. But the trend was not uniform.

The bio-chemical investigations played a very vital role for proper diagnosis of the pregnant mothers for preeclampsia. Serum Albumin test, a liver function test, measures the amount of albumin in clear liquid portion of blood that was generated by liver. Fairly lower values of serum albumin (average 1.54 g/dL) were observed in all the preeclamptic mothers. This indicates the increase in plasma volume that occurs during the pregnancy leading to hemodilution. The observed slight lower values of serum urea (average 5.92 mmol/L) and blood urea nitrogen (BUN) (average 17 mg/dL) reflected higher possibility of low-birth weight (LBW) neonatal output. The observed relatively higher values of serum creatinine (> 0.8 mg/dL) suggested intravascular volume contraction or renal involvement in preeclampsia. The relative lower values of platelet count (average 2.34 million/mm^3) threw light on the presence of mild preeclampsia. The fairly lower values of hemoglobin (average of 9.02 g/dL) reflected that the studied preeclamptic mothers are highly anemic. Thus, they were under greater risk of preeclampsia, preterm delivery, LBW and stillbirth. The random blood sugar (R.B.S.) levels of the preeclamptic mothers were not very elevated (6.10%) reflecting that the patients were not under diabetics and this was important to ensure the best chance of a successful pregnancy.

The preeclamtic patients were confirmed based upon patients' B.P., edema and serum albumin along with physiological complications and other laboratory investigations. For drug management purpose Methyldopa, Nifedipine, Labetalol, Magnesium sulfate and Phenobarbital were applied.

The maximum and minimum gestational ages during delivery were 40 and 32 weeks respectively, averaging 37 weeks. About three-fourths of the patients'

deliveries were made by C/S, while the rest by NVD. Two patients were released for being admitted into other hospital. In general, after delivery, the concerned mothers' health conditions were good, whereas new-born infants' condition were bad. But before delivery, the mothers' conditions were bad.

It was found that out of 88 patients, one had died after giving birth (that generated maternal morbidity rate of 1.14%), which was probably due to conversion to severe eclampsia or HELLP syndrome. It was interesting to note that her female infant (weighing 2.0 kg) was in good condition. Only one case of twin-pregnancy was recorded. The new-born infants were both female and in good health conditions having weights of 3.0 and 2.5 kg. With regard to maternal heath after giving births, 28% had no complications, whereas the remaining (72%) had either mild or severe complications.

Male children dominated (about 60%) over female children (about 40%) in case of preeclamptic mothers. In the study, a total of 9 neonatal deaths were recorded out of 88, representing 10.23% of total. Among the alive infants, 41.77% were premature having body weight of < 2.5 kg, while the rest (58.23%) were with standard health (≥ 2.5 kg). About 28% of the newly born infants had no complications, while the rest (72%) were under mild or severe complications. Such complications included Asphyxia, IUGR, etc.

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LIST OF ABBREVIATIONS

ABPM	Ambulatory Blood Pressure Monitoring
ACE	Angiotensin Converting Enzyme
ACOG	American College of Obstetricians and Gynecologists
ACR	Albumin : Creatinine Ratio
AFM	Atomic Force Microscope
ALT	Alanine transaminase
ANC	Antenatal Care
AOR	Adjusted Odds Ration
aPTT	Activated Partial Thromboplastin Time
ART	Assisted Reproductive Technology
AST	Aspartate transaminase
BID	Twice daily dosing
BMI	Body Mass Index ($kg\ m^{-2}$)
BP	Blood Pressure (mm of Hg)
BUN	Blood Urea Nitrogen (mg/dL)
CBC	Complete Blood Count
CI	Confidence Interval
C/S	Cesarean Section
CVA	Cerebral Vascular Accident
dB	Decibel (unit of sound)
dBP	Diastolic Blood Pressure
DE&C	Dilatation, Evacuation and Curettage

DIC	Disseminated Intravascular Coagulation
DoE	Department of Environment
DPHE	Department of Public Health Engineering (Bangladesh)
FHR	Fetal Heart Rate
GFR	Glomerular Filtration Rate
HDL	High-density Lipoprotein
HDP	Hypertensive Disorders of Pregnancy
HELLP	Hemolysis, Elevated Liver enzymes and Low Platelet count
HICs	High Income Countries
HIES	Household Income and Expenditure Survey
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
HSC	Higher Secondary Certificate
IARC	International Agency for Research on Cancer (France)
INR	International Normalized Ration
ITP	Immune Thrombocytopenic Purpura
IUGR	Intra-uterine Fetal Growth Restriction
IV	Intravenous
JSC	Junior School Certificate
LBW	Low Birth Weight
LDH	Lactate dehydrogenase
LGA	Large-for-gestational Age
LMICs	Low and Middle Income Countries

MB	Maternal Blood
mm Hg	Millimeter of Mercury
mRNA	Messenger Ribonucleic acid
NVD	Normal Vaginal Delivery
OPD	Out Patient Department
OR	Odds Ratio
PAPP-A	Pregnancy-associated Plasma Protein-A
PE	Preeclampsia
PEC	Primary Education Completion
PHE_2	Prostaglandin
PI	Pulsatility Index
PlGF	Placental Growth Factor
PRES	Posterior Reversible Leukoencephalopathy Syndrome
QID	Four times daily dosing
RBC	Red Blood Cell
RBS	Random Blood Sugar
RI	Resistance Index
RIND	Reversible Neurological Deficit
RMCH	Rajshahi Medical College Hispital (Rajshahi, Bangladesh)
RUQ	Right Upper Quadrant
SAP	Shrimp Alkaline Phosphatase
sBP	Systolic Blood Pressure
SBV	Stem Blood Vessel
SCs	Syncytiotrophoblastic Cells

SEI	Socio-economic Index
sFlt-1	Soluble Fms-like Tyrosine Kinase
SGA	Small-for-gestational Age
SGOT	Serum Glutamic oxaloacetic transaminase
SGPT	Serum lutamic pyruvic transaminase
SOGC	Society of Obstetrics and Gynaecologists of Canada
SSC	Secondary School Certificate
TIA	Transient Ischaemic Attack
TID	Three times daily dosing
TTP	Thrombotic Thrombocytopenic Purpura
UNDP	United Nations Development Program
USEPA	United States Environmental Protection Agency
UTI	Urinary Tract Infection
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

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CHAPTER ONE :

INTRODUCTION

1.1 INTRODUCTION

Pregnancy or gestation is the period from concept to birth of a child and it is the time during which one or more offspring develops inside a woman. The ovum is fertilized by a sperm and then implanted in the lining of the uterus, it develops into the placenta and embryo and later to a fetus. Pregnancy usually lasts 40 weeks beginning from the first day of the woman's last menstrual period. It is divided into three trimesters, lasting three months each.

About 213 million pregnancies occurred in 2012 of which 190 million were in the developing world and 23 million were in the developed world. In 2013, complications of pregnancy resulted in 293 thousands deaths. The causes of maternal death were bleeding, complications of abortion, high blood pressure, puerile sepsis and obstructed labor.

Preeclampsia is a multi-system obstetrical disorder of unknown etiology characterized mainly by development of hypertension to the extent of 140/90 mm of Hg or more with proteinuria (protein in urea) that can develop into tonic-clonic seizures after the 20^{th} week in a previously normotensive and non-proteinuric women.

The most commonly cited and accepted estimate of hypertensive disorder of pregnancy is 5–10% (Cunningham et al., 2009). World Health Organization's (WHO) multicountry survey reported an overall prevalence

of preeclampsia of 2.2%, ranging from 1.4% in the Middle East region to 3.9% in the African region (Abalos *et al.*, 2014). Other cohorts reviewed since 1995 reported the prevalence ranging from 1.2% to 8.4%. In another WHO systematic review of 129 studies covering approximately 39 million women from 40 countries (2002–2010), the crude incidence of preeclampsia was 2.3% (4.6% using a model-based estimation), ranging from 1.2% in the Middle East to 4.2% in the Western Pacific (Abalos *et al.*, 2013). However, there was substantial regional variation, from 0.7% reported in a small study from Morocco to 15.6% reported in a Turkish data set.

Preeclampsia is one of the top five causes of maternal and perinatal mortality worldwide. Preeclampsia claims the lives of more than 70,000 women and more than 500,000 of their fetuses and newborns each year. This is equivalent to the loss of 1,600 lives per day (Firoz *et al.*, 2011).

But the origin of preeclampsia remains still elusive. One genesis is the result of reduced placental perfusion and another result from maternal disorders pre-existing pregnancy. These pre-existing maternal disorders comprise predisposing factors for cardiovascular disease such as hypertension, renal disease, overweight, and diabetes (Ness and Roberts, 2005). Over the last two decades, the evidence to support this hypothesis has grown, leading more to preeclampsia being a pregnancy-specific inflammatory disorder of variable pathogenesis.

Irrespective of the origin, preeclampsia acts a gestational hypertensive disorder commonly defined by new-onset proteinuria, and possibly other adverse conditions leading to typical end-organ dysfunction (Magee *et al.*, 2016). Preeclampsia always presents potential danger to both the mothers and babies. Sometimes, mild preeclampsia (especially if remains untreated) can progress into severe preeclampsia.

The principal signs and symptoms of preeclampsia include high blood pressure (≥140/90), elevated levels of proteinuria (consists of Tamm-Horsfall protein and albumin) and, edema (swelling) of face and legs. The other signs and symptoms include severe headaches, changes in vision (temporary loss of vision, blurred vision or light sensitivity), upper abdominal pain (usually under the ribs on the right side), nausea or vomiting, decreased urine output, decreased levels of platelets in blood (thrombocytopenia), impaired liver function, shortness of breath (caused by fluid in lungs).

There are numerous risk factors of preeclampsia. Both maternally and paternally derived fetal genes might play a significant role in the development of the disease (Trogstad *et al.*, 2011). Those women who experienced preeclampsia earlier, the rate of disease was higher in sisters (37%), daughters (26%) and grand-daughters (16%) (Chesley and Cooper, 1986). Extremes of maternal ages (≤19 and ≥40 years) have been associated with risk of preeclampsia (Redman and Sargent, 2005). The risk of preeclampsia increased to four-fold for those women who weighed <2500 g

at birth and were overweight or obese as adults (Dempsey *et al.*, 2003). Pre-gestational diabetes (type 1 and 2) is associated with two- to four-fold increased risk of the disease (Sibai *et al.*, 2000; Feig *et al.*, 2006). Preeclampsia may occur frequently in pregnant women with chronic kidney disease and lupus nephropathy (Hirose *et al.*, 2014). Nulliparous women were at increased risk of preeclampsia compared with parous women (Odegard *et al.*, 2000). The risk of preeclampsia is generally lower in the second pregnancy if conceived with the same partner. For women who had recurrent spontaneous abortions and infertility treatment, a three-fold increased risk of preeclampsia was seen compared with controls (Trogstad *et al.*, 2009). Women with twin pregnancy had higher rates of gestational hypertension and preeclampsia (Sibai *et al.*, 2000). Women with a urinary tract infection (UTI) and those with periodontal disease were more likely to develop preeclampsia. Epidemiological studies suggest that the risk for preeclampsia doubles if the woman has a partner aged >45 years (Chen *et al.*, 2006; Dekker *et al.*, 2011), perhaps as a result of spermatozoa being damaged owing to genetic mutations. It is surprising that smoking, although having adverse health effects, during pregnancy approximately halves the risk of preeclampsia (England and Zhang, 2007). High levels of physical activity during pre-pregnancy and pregnancy were less likely to develop it (Aune *et al.*, 2014). Depression and anxiety in the first trimester of pregnancy are known to increase the risk of preeclampsia by two- to three-fold (Kurki *et al.*, 2000). Severe anaemia (haemoglobin <70 g/L) was associated with a three-fold greater risk of preeclampsia (Bilano *et al.*, 2014).

The complications of preeclampsia may include fetal growth restriction, preterm birth, placental abruption, HELLP syndrome, eclampsia, organ damage and cardiovascular disease (Saxena, 2014). The diagnosis of preeclampsia are - a) physical examinations (elevated blood pressure, excessive weight gain, edema, headache and visual problems, upper abdominal pain and ankle clonus), b) altered renal function examination (proteinuria, serum creatinine, uric acid, blood urea nitrogen), c) altered liver function examination (liver enzymes like ALT, AST, bilirubin and GGT, LDH), d) examination of hematologic abnormality (hemoglobin and hematocrit, platelet count, plasma fibrinogen) and e) doppler ultrasound evaluation.

The preventative interventions may be best started before 16 weeks' gestation when most of the physiologic transformation of uterine spiral arteries occurs, or even before pregnancy. Such early intervention has the greatest potential to decrease the early forms of preeclampsia that are associated with incomplete transformation of uterine spiral arteries (Ogge et al., 2011). The generally accepted recommendations include the followings: abstention from alcohol, low-dose aspirin intake, high-dose calcium intake, low-to moderate-intensity regular exercise (Mozurkewich et al., 2000), vitamin D supplementation, magnesium as a micronutrient supplementation (300 mg/d) (Bullarbo et al., 2013).

The major objectives of management of preeclampsia are to stabilize hypertension, to prevent the observed complications, to prevent further eclampsia, to deliver a healthy baby in optimal time and to restore the health

of the mother in puerperium. For these, the following steps are suggested: 1) assessment on mild or severe preeclampsia, 2) decision on hospital or home treatment, 3) hospital management (rest, diet, diuretics, antihypertensives), 4) monitoring of maternal and foetal conditions, 5) determination of time and mode of delivery, and 6) continuation of postpartum care.

Despite a great deal of research, the origin of preeclampsia is still elusive. To the best of our knowledge, in Bangladesh there is no comprehensive data on the impact of some risk factors of preeclampsia. Especially the environmental pollutants, external stress and climate change are not yet addressed. In addition, the prevalence of the life-threatening phenomena should be estimated properly. Besides these, relation between placental etiology of preeclampsia mother and severity of preeclampsia is not well studied in Bangladesh. This reflects the necessity of the present investigation.

The general objectives of the present study are to estimate the prevalence of preeclampsia, to identify the potential risk factors associated with it, so that recommendations can be put forward to identify the factors at the earliest possible.

It is believed that after completion of the research the factors that lead to minimization of preeclampsia will be established. That is, the diagnosis for management of preeclampsia will be improved. Thus, the outcome will help to ensure the safety of the mothers and new-born babies.

CHAPTER TWO :

RATIONALE, HYPOTHESIS AND OBJECTIVES

2.1 RATIONALE

Hypertension is defined by a sustained systolic blood pressure (sBP) of ≥140 mm Hg or a sustained diastolic blood pressure (dBP) ≥90 mm Hg, by office (or in hospital/clinic). But defining 'hypertension in pregnancy' is challenging, because blood pressure levels in pregnancy are dynamic, having a circadian rhythm that changes with advancing gestational age. Hypertensive disorders complicate 5–10% of pregnancies worldwide (Magee *et al.*, 2016). Hypertensive disorders of pregnancy can be classified into Pre-existing (Chronic) Hypertension, Gestational Hypertension, Preeclampsia and White Coat Hypertension. Among these, Preeclampsia have the greatest risk of maternal and perinatal complications, leading to significant death of mothers and babies. Therefore, appropriate screening for 'hypertension in pregnancy' using standard tools and techniques as well as international guidelines are very important.

Pre-eclampsia remains one of the top five causes of maternal and perinatal mortality worldwide. Preeclampsia claims the lives of more than 70,000 women per year and more than 500,000 of their fetuses and newborns (Firoz *et al.*, 2011). This is equivalent to the loss of 1,600 lives per day. More than 99% of these losses occur in low- and middle-income countries (LMICs), particularly those on the

Indian subcontinent and sub-Saharan Africa (Khan *et al.*, 2006a). For every woman who dies, it is estimated that another 20 suffer a life-altering morbidity (Pattinson and Hall, 2003; Ghulmiyyah and Sibai, 2012). It is to be noted that the maternal and perinatal deaths and sequelae result primarily from delays in triage, transport and treatment.

Once preeclampsia is present, there is no definite cure other than to deliver the foetus. Other complications include stroke of brain, placental abruption, cardiovascular disease, HELLP syndrome, premature birth, hemorrhage, etc. (Mayo Clinic, 2018). Thus preeclampsia is life-threatening to both mother and foetus. Since preeclampsia induced complications are difficult to diagnosis, are multi-directional and inter-liked, appropriate management of such patients are challenging.

Despite a great deal of research, the origin of preeclampsia is still elusive. To the best of our knowledge, in Bangladesh there is no comprehensive data on the impact of some risk factors of preeclampsia. Especially the environmental pollutants, external stress and climate change are not yet addressed. In addition, the prevalence of the life-threatening phenomena should be estimated properly. Besides these, relation between placental etiology of preeclampsia mother and severity of preeclampsia is not studied in Bangladesh. This reflects the necessity of our investigation.

2.2 OBJECTIVES

2.2.1. General Objective

The general objective of the study is to estimate the prevalence, to identify the potential risk factors and to recommend proper diagnosis for management of preeclampsia.

2.2.2. Specific Objectives

The specific objectives of the study include the followings:

- To find out the prevalence of preeclamptic patients admitted into Rajshahi Medical College Hospital and its nearby hospitals/clinics.
- To investigate the potential risk factors of preeclampsia in Rajshahi region.
- To understand how external stresses affect preeclampsia.
- To assess bio-social factors of the concerned mothers.
- To assess how environmental pollution affects preeclampsia.
- To characterize placenta with respect to mode of delivery.
- To understand the changes of gynecological and obstetrical phenomena due to preeclampsia.
- To understand the relationship between foetal and maternal outcome along with mode of delivery.
- To recommend the proper diagnostic methods towards proper management of preeclampsia.

2.3 RESEARCH HYPOTHESIS

The hypothesis or assumptions on which the investigations were based are discussed below**:**

1) Among the pregnancy induced hypertensive patients visiting OPD or admitted into the hospitals and clinics, preeclampsia is vulnerable, especially in winter season**.**
2) Environmental pollutions should have an adverse impact on the pregnant women towards facilitating preeclampsia**.** Among the pollutants, groundwater contaminants, sounds louder than 70 dB and CO_2 exposure should bear significance**.**
3) Mental stress of pregnant mother should induce preeclampsia**.**
4) There should be a change in peripheral structure in membrane of placenta originated from preeclamtic mother**.**
5) With the increasing literary rate in Bangladesh, the patients should be more conscious about their diets during pregnancy**.**
6) Socio-economic index is very important for evaluating preeclampsia; because roughly lower social class should be highly exposed to preeclampsia**.**
7) Family medical history is important for preeclamptic patients**.**
8) After delivery or C/S, the mother's conditions should be good, while the infant's condition might not be good**.**

2.4 Scope Of The Study

The screening of pregnancy induced hypertensive patients for preeclampsia is a challenge, since a lot of variables are involved. In order to ensure the proper screening or diagnosis processes, only a few hospitals and clinics were selected where quality control could be assured following international obstetrical standard. Among these Rajshahi Medical College Hospital (RMCH) - the tertiary referral hospital - was our prime concern. The selected other six hospitals and clinics are of the desired standard (please refer to section 3.4). These hospitals/clinics have the modern facilities with cross-checking facility of a parameter by several ways and are situated within the studied area.

It was beyond the scope to characterize the groundwater that the preeclamptic patients take as drinking water in their regions under this study directly. In 2001, British Geological Survey (BGS, 2001) made an extensive countrywide groundwater survey (n = 3,534) in Bangladesh. We utilized their dataset to understand the relation between the extent of groundwater contaminants and preeclampsia.

Sometimes a preeclamtic patient could not be monitored or followed up completely in a specific hospital/clinic for her migration.

To solve the problem, verbal communication through cell phones of the patient and her attended was made. It is to be noted that the Central Science Laboratory of Rajshahi University, Bangladesh facilitated the peripheral view of placenta through Fluorescence Illuminator Research Inverted System 'Biological Microscope'. We had access to the sophisticated instruments in the Microbiological/Pathological Departments of the concerned hospitals or clinics.

CHAPTER THREE :

REVIEW OF LITERATURE

3.0 Review Of Literature

3A Preeclampsia As a Disease

3.1 Definition of Preeclampsia

Preeclampsia is a gestational hypertensive disorder commonly defined by new-onset proteinuria, and possibly other adverse conditions leading to typical end-organ dysfunction (Magee *et al.*, 2016). The 'adverse conditions' associated with preeclampsia consist of maternal symptoms and signs, abnormal maternal laboratory results, and abnormal fetal monitoring results that may herald the development of more severe complications. They are conditions to which we respond (e.g., low oxygen saturation) in order to avoid end-organ complications of preeclampsia (e.g., pulmonary edema) (Gillon *et al.*, 2014).

Hypertension in pregnancy is a major contributor to maternal and perinatal mortality and morbidity. Preeclampsia remains one of the top five causes of maternal and perinatal mortality worldwide. Every year preeclampsia claims the lives of more than 70,000 women and more than 500,000 of their fetuses and newborns. This is equivalent to the loss of 1,600 lives per day (Firoz *et al.*, 2011). More than 90% of these losses

occur in low- and middle-income countries (LMICs), particularly those on the Indian subcontinent and sub-Saharan Africa (Khan *et al.*, 2006). For every woman who dies, it is estimated that another 20 suffer a life-altering morbidity (Ghulmiyyah and Sibai, 2012). Those who survive, especially those who had preterm preeclampsia, face the issues of hypertensive, cerebro- and cardiovascular events in the future resulting in premature deaths.

3.2 Classification of Hypertensions

Generally, hypertension refers to a sustained systolic (sBP) of ≥ 140 mm Hg or a sustained diastolic blood pressure (dBP) ≥ 90 mm Hg, by office (or in-hospital) measurement. But defining hypertension in pregnancy is challenging, because blood pressure levels in pregnancy are dynamic, having a circadian rhythm and also changing with advancing gestational age (Figure 1). A sustained rise of blood pressure to 140/90 mm of Hg or more on at least two occasions four or more hours apart beyond the 20th week of pregnancy or within the first 48 hours of delivery in a previously normotensive woman is called Gestational Hypertension (Konar, 2016).

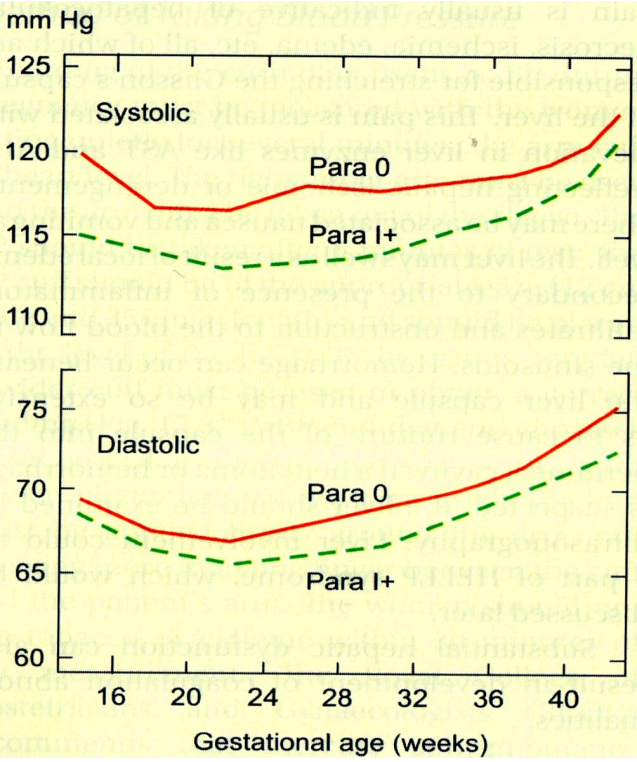


Figure 1. Changes in systolic and diastolic blood pressures in relation to gestational age during normal pregnancy (Saxena, 2014).

The classification of hypertension by National Institute for Health and Care Excellence of UK (NICE, 2017) based on its severity is summarized in Table 1**.**

Table 1. Classification of hypertension based on degree of severity**.**

Degree of Hypertension	**Systolic B.P.* (mm Hg)**	**Diastolic B.P. (mm Hg)**
Mild	140 – 149	90 – 99
Moderate	150 – 159	100 – 109
Severe	≥ 160	≥ 110
Hypertensive emergency (crisis)	≥ 180	≥ 120 (evidence of impending or progressive target organ dysfunction)
Hypertensive urgency	≥ 180	≥ 120 (no progressive target organ dysfunction)

* B.P. stands for blood pressure

3.3 Classification of Hypertensive Disorders in Pregnancy

According to The American College of Obstetricians and Gynecologists (2013), the classification of hypertensive disorders in pregnancy can be represented in the following flow chart (Figure 2).

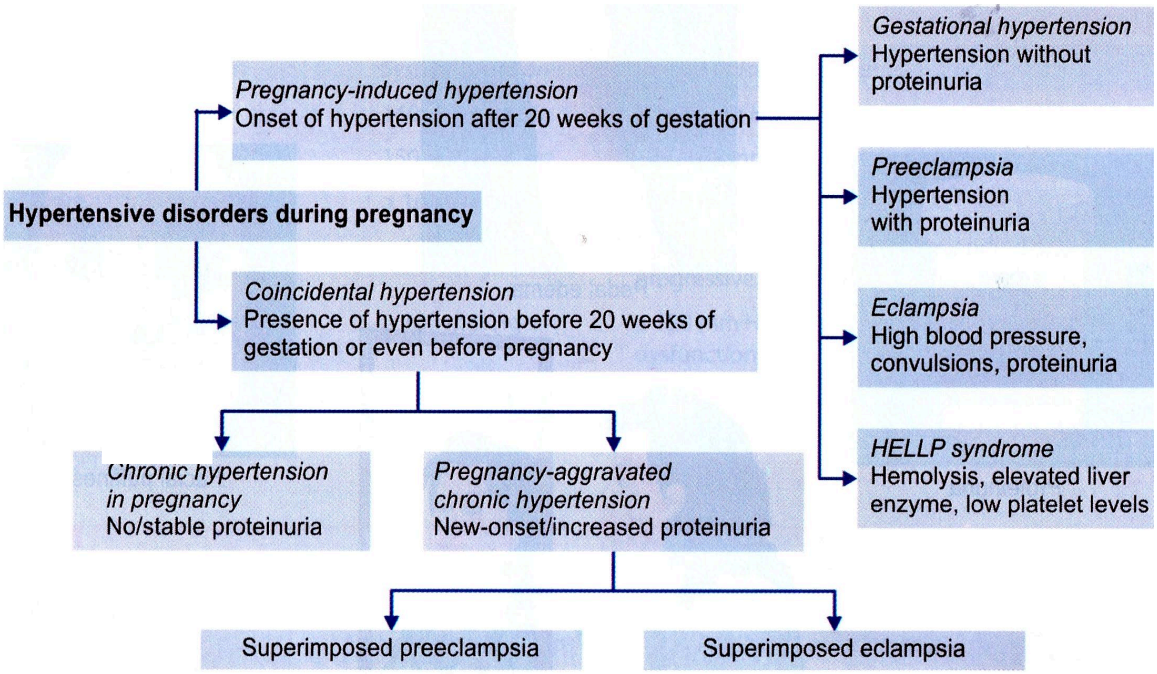


Figure 2. Classification of hypertensive disorders in pregnancy.

Based upon the characteristic clinical features, hypertensive disorders in pregnancy can also be classified as Table 2 (Saxena, 2014).

Table 2. Classification of hypertensive disorders in pregnancy.

Type of disorder	Characteristics
Gestational hypertension	• Appearance of high BP (> 140/90 mm Hg) for the first time during pregnancy after 20 weeks of gestation • No proteinuria • BP returns to normal within 12 weeks of postpartum period

Cont…

Type of disorder	Characteristics
Preeclampsia / eclampsia	● Appearance of high BP (> 140/90 mm Hg) for the first time during pregnancy after 20 weeks of gestation ● Presence of proteinuria (> 300 mg/L or > 1+ on the dipstick) ● BP returns to normal within 12 weeks of postpartum period ● Eclamsia is the occurrence of seizures in a pregnant woman with preeclampsia
Chronic hypertension	● Appearance of high BP (> 140/90 mm Hg) before 20 weeks of gestation or even before pregnancy ● No proteinuria ● BP does not return to normal within 12 weeks of postpartum period
Preeclampsia superimposed on chronic hypertension	● New-onset proteinuria in woman with presence of hypertension and no proteinuria early in pregnancy (< 20 weeks) ● A sudden increase in BP in a woman whose hypertension has previously been well controlled ● Thrombocytopenia (platelet count < 100,000 cells/mm^3) ● An increase in alanine transaminase (ALT) or aspartate transaminase (AST)

3.3.1. Gestational Hypertension: It is defined as hypertension that appears at $\geq 20^{+0}$ weeks, without the occurrence of proteinuria**.** However, using ambulatory blood pressure monitoring (ABPM), a 'white coat' effect is seen among about 30% of women diagnosed with hypertension at ≥20

weeks, and this rises to approximately 70% by the third trimester (Magee *et al*., 2008)**.** Women with gestational hypertension have maternal and perinatal risks that are highly dependent on the gestational age at presentation and the progression to pre-eclampsia**.** When gestational hypertension appears before 34^{+0} weeks, approximately 35% of women develop pre-eclampsia with the associated heightened risks of maternal and perinatal complications (Saudan *et al.*, 1998; Barton *et al.*, 2001; Brown and Buddle, 2002; Magee *et al.*, 2003)**.** Development of that preeclampsia takes an average of about 5 weeks**.**

3.3.2. Pre-existing or Chronic Hypertension: It is defined as that which either pre-dates pregnancy or appears before 20^{+0} weeks of pregnancy**.** Pre-existing hypertension is associated with adverse outcomes for both mother and baby**.** For the mother, the following risks are heightened: superimposed preeclampsia (approximately 20%) (Ferrazzani *et al.*, 1990; Rey and Couturier, 1994; Ananth *et al.*, 1995; Haelterman *et al.*, 1997; Clausson *et al.*, 1998; Lydakis *et al.*, 1998; Ray *et al.*, 2001; Bagga *et al.*, 2007; Chappell *et al.*, 2008), half of which develops at term, preterm delivery (about 3 3%), and placental abruption (1**.**8%)**.** Babies born to women with pre-existing hypertension are also at increased risk of acute or chronic hypoxia/acidosis**.** Approximately 15% of these babies are born small for gestational age

(SGA) (Ferrazzani *et al.*, 1990; Rey and Couturier, 1994; Haelterman *et al.*, 1997; Brown and Buddle, 2002; Chappell *et al.*, 2008). In a secondary analysis of women with singleton pregnancies and chronic hypertension diagnosed before 20 weeks in the National Institutes of Child Health and Development aspirin trial (Caritis *et al.*, 1998), the risks of adverse pregnancy outcomes increased with increasing blood pressure (Ankumah *et al.*, 2014).

It is important to recognize that stillbirth risk reaches 0.1% by 36 weeks in pregnancies complicated by hypertension, similar to that reached at 41 weeks in low-risk pregnancies to justify labour induction (Hutcheon *et al.*, 2011). Up to 50% of these newborns are admitted to high-level NICU care because of short-term complications, such as hypothermia, respiratory failure and feeding problems.

It is widely recognized to be the hypertensive disorder of pregnancy associated with the greatest maternal and perinatal risks, particularly when it is severe in nature and/or presents before 34 weeks. In the latter case, a stillbirth rate of about 10% and a perinatal mortality rate of at least 5% have been reported (Brown *et al*., 2001). The risk of small-for-gestational age (SGA) is also primarily concentrated in cases presenting at <34 weeks, while there is an increased number of large-for-gestational age (LGA) fetuses at term 37–39.

3.3.3. Preeclampsia: All hypertension societies consider preeclampsia as a gestational hypertensive disorder commonly defined by new-onset proteinuria, and possibly other adverse conditions leading to typical end-organ dysfunction (Magee *et al.*, 2016)**.** The adverse condition' associated with preeclampsia consist of maternal symptoms and signs, abnormal maternal laboratory results, and abnormal fetal monitoring results that may herald the development of more severe complications**.**

3.3.4. White Coat Hypertension: In Canada, in 2014, a new category of 'other' was added to the classification system**.** *'White coat' hypertension* is seen when blood pressure is elevated in the office, but normal by ambulatory blood pressure monitoring (ABPM) or at home**.** White coat effect in early pregnancy is common (approximately 30%), similar to estimates outside of pregnancy (Rey *et al.*, 2009)**.** The limited literature suggests that there is a heightened risk of adverse maternal outcomes compared with normotensive pregnancy, but the risks are probably smaller than with pre-existing hypertension (Brown *et al.*, 2005)**.** Of these women, 40% progress to gestational hypertension and 8% to preeclampsia**.**

3.3.5. Masked Hypertension: It refers to blood pressure that is normal in the office but elevated by ABPM or at home**.** Masked hypertension may be present in about 30% of women with pre-existing hypertension (Rey *et al.*,

2009). However, the associated perinatal risks are unknown. Outside pregnancy, cardiovascular risk associated with masked hypertension is similar to that associated with sustained hypertension. Masked gestational hypertension was seen in 4–15% of women in prospective cohort studies; pregnancy outcomes were similar to those of women with sustained gestational hypertension (Hermida *et al.*, 2003; Eguchi *et al.*, 2015).

3.4. Clinical Classification of Preeclampsia: The clinical classification of preeclampsia based on its time of onset (prior to 34 weeks or after 34 weeks) has been described in Table 3.

Table 3. Clinical classification of preeclampsia (Saxena, 2014).

Characteristics	**Early onset preeclampsia**	**Late onset preeclampsia**
Underlying etiology	Placental dysfunction	Underlying maternal constitutional factors
Placental volume	Reduction in placental volume	Normal or larger placental volume
Fetal growth	Intrauterine growth restriction	Normal fetal growth
Uterine and umbilical artery Doppler evaluation	Abnormal	Normal
Baby's birth weight	Low	Normal
Maternal and neonatal outcome	Usually adverse	More favorable
Maternal and fetal morbidity	More	Less

Preeclampsia always presents potential danger to the mother and baby. Sometimes, mild preeclampsia (especially if remains untreated) can progress into severe preeclampsia. Difference between mild and severe preeclampsia is listed in Table 4. Severe preeclampsia may ultimately result in development of eclampsia, which can be defined as the occurrence of seizures, which cannot be attributed to other cause, in a woman with preeclampsia.

Table 4. Difference between mild and severe preeclampsia (Saxena, 2014).

Characteristics	*Mild preeclampsia*	*Severe preeclampsia*
Time of presentation	Presents at gestational age ≥ 34 weeks	Presents at gestational age < 34 weeks
Diastolic BP	< 100 mm Hg	> 110 mm Hg
Symptoms showing neurological involvement such as headache, visual disturbances, hyperreflexia, etc. and abdominal pain	Absent	May be present
Presence of ominous features such as convulsions (eclampsia), congestive heart failure or pulmonary edema	Absent	May be present
Oliguria	Absent	Present
Elevated liver enzymes (LDH, AST)	Absent	Present
Thrombocytopenia (platelet count < 1,00,000 per µL)	Absent	May be present
Serum creatinine levels	Normal	Elevated
Proteinuria	Mild to moderate	Severe (in nephrotic range) > 3 g/24 hours (especially in association with ominous features
Non-reassuring fetal heart rate with or without fetal growth restriction	Absent	Present
Abbreviations: LDH, lactate dehydrogenase; AST, aspartate transaminase		

3.5 Signs and Symptoms of Preeclampsia

The signs and symptoms of preeclampsia are mentioned below**:**

High Blood Pressure (B.P.): High blood pressure (≥140/90) during pregnancy is one of the biggest red flags that preeclampsia may be developing**.** Even if it is not a potential symptom of preeclampsia, it can still be a sign of a problem**.** If one has high B.P., or hypertension, the heart has to work harder to pump the blood around the body, that can affect the heart muscle**.** The reasons for high B.P. include sedentary life leading, eating unhealthy foods and salts, mental stress, environmental pollution, etc**.** It is important to note that lowering the B.P. by taking drugs can reduce the blood flow to the placenta and to the baby (NHS, 2018)**.**

Proteinuria (Protein in Urine): Proteinuria consists of Tamm-Horsfall protein (most abundant) as well as albumin, thyroxine-binding prealbumin, immunoglobulins, α1-antitrypsin, transferrin, β-lipoprotein and low-molecular weight proteins (Conrad and Lindheimer, 1999)**.** During normal pregnancy, proteinuria increases through the trimesters, from 0**.**15 g/d to 0**.**3 g/d**.** This is attributable to the increase in renal plasma flow and glomerular filtration rate, as well as changes in protein handling in the nephron (Conrad and Lindheimer, 1999)**.** Preeclampsia affects the glomeruli, and the lesion has been termed '**glomerular endotheliosis**'**.** This terms describes glomerular endothelial swelling and loss of the integrity of the fenestrae

(i.e., sieving apparatus), leading to leakage of protein into the renal tubules and associated occlusion of the capillary lumens (Stillman and Karumanchi, 2007). Hence proteinuria is a significant sign of preeclampsia. Clinical measurement values by Dipstick of Trace, 1+, 2+, 3+ and 4+ corresponds to 0.01 (negative), 0.3 (weakly positive), 1.0 (positive), 3.0 (strongly positive) and 10.0 (strongly positive) g protein L^{-1} urine (Saxena, 2014; Magee *et al.*, 2016).

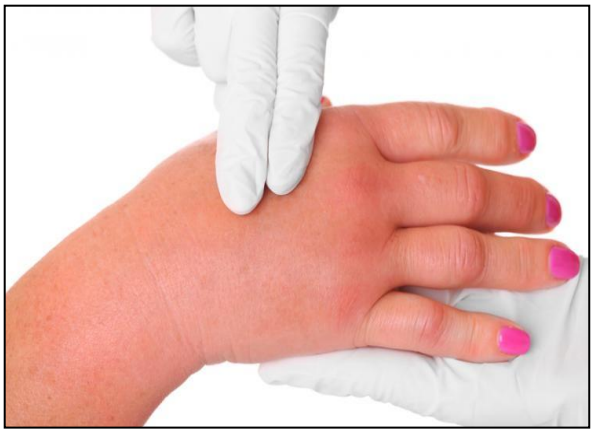
Edema (Swelling): A certain amount of swelling is normal during pregnancy. Edema, on the other hand, is the accumulation of excess fluid, and can be a concern when it occurs in face, around eyes, or in hands. This is one of the symptoms of preeclampsia.

The other signs and symptoms of preeclampsia (Figure 3) may include the followings (Mayo Clinic, 2018):

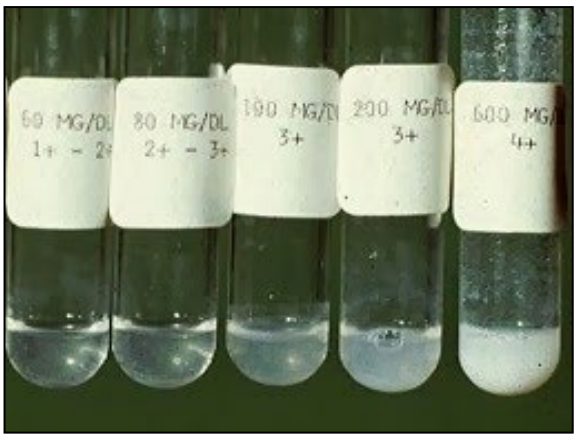
- Severe headaches
- Changes in vision, including temporary loss of vision, blurred vision or light sensitivity
- Upper abdominal pain, usually under the ribs on the right side
- Nausea or vomiting
- Decreased urine output
- Decreased levels of platelets in blood (thrombocytopenia)
- Impaired liver function
- Shortness of breath, caused by fluid in lungs

Severe headaches

Nausea or Vomiting



Swelling (Edema)



Proteinuria (Protein in urea)

High Blood Pressure (≥140/90 mmHg)

Shortness of Breath

Upper Abdominal or Shoulder Pain

Blurred Vision

Figure 3. Some sign and symptoms of preeclampsia (Magee *et al.*, 2016; Mayo Clinic, 2018)**.**

3.6 Origin of Preeclampsia

The cause of preeclampsia remains elusive in spite of many attempts to understand its biologic characteristics and to characterize its predictors**.** Ness and Roberts (2005) suggested several distinct origins of preeclampsia, each with its own pathologic characteristics and natural history**.** One genesis is the result of reduced placental perfusion and another result from maternal disorders pre-existing pregnancy**.** These pre-existing maternal disorders comprise predisposing factors for cardiovascular disease such as hypertension, renal disease, overweight, and diabetes (Ness and Roberts, 2005)**.** Over the last two decades, the amount of evidence to support this hypothesis has grown, leading more to preeclampsia being a pregnancy-specific inflammatory disorder of variable pathogenesis (Figure 4)**.**

Angiogenic factor imbalance, with an excess of circulating anti-angiogenic factors (e.g., soluble fms-like tyrosine kinase (sFlt)-1 and soluble endoglin) and a reduction in pro-angiogenic factors (e.g., placental growth factor (PlGF)), has a clear role in identifying pregnancies complicated by placental underperfusion, be that manifested as preeclampsia or normotensive intrauterine growth restriction (Maynard and Karumanchi, 2011; Benton *et al.*, 2012)**.** This angiogenic imbalance appears to be predictive of early-onset (at or before 34 weeks of pregnancy), primarily placental underperfusion-related, preeclampsia that is more dangerous to the individual woman with the condition, as demonstrated in both well- and under-resourced settings (von Dadelszen *et al.*, 2011)**.** It may be of particular importance in identifying women with pre-existing medical conditions, especially renal disease, who have developed superimposed preeclampsia (Bramham *et al.*, 2015)**.** It is unclear why some women with

angiogenic factor imbalance develop preeclampsia, while others remain normotensive, but the concentration of circulating placental debris may be an example of an important co-factor in stimulating the clinical syndrome of preeclampsia (Goswami *et al.*, 2006).

Late-onset preeclampsia is more closely related to factors that predict later cardiovascular disease through the metabolic syndrome (Kenny *et al.*, 2014), the so-called "maternal preeclampsia". Reflecting these findings, point-of-care assessment with glycosylated fibronectin, a strong marker of the risk of gestational diabetes and management, may provide a readily available method of confirming the diagnosis of "maternal" preeclampsia (Rasanen *et al.*, 2015).

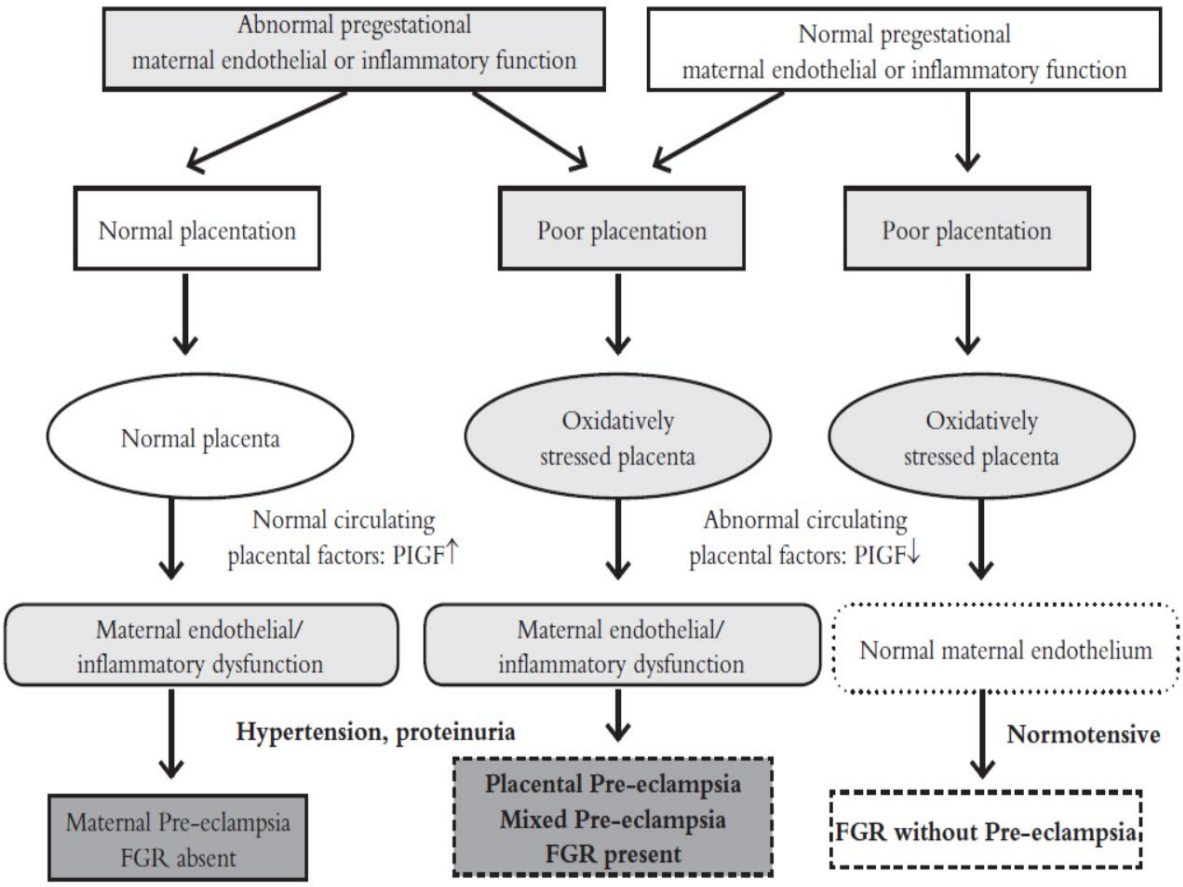


Figure 4. A model of preeclampsia (Staff *et al.*, 2013).

3.7 Risk Factors of Preeclampsia

Risk factors are any attributes or exposures that increase the chances for an individual to develop a disease**.** Risk factors for preeclampsia include a wide array of conditions that reflect the complexity of the disease process and their strengths of association are quantified using risk ratios or odds ratios**.** These can be categorized based on familial factors, demographic factors, past medical or obstetric history, pregnancy-associated factors, paternal factors and miscellaneous factors**.**

3.7.1. Familial Factors: Preeclampsia is a complex disorder, which is seen to be inherited in a familial pattern**.** The placenta plays a central role in the pathogenesis of preeclampsia, thus implying that both maternally and paternally derived fetal genes may play a role in the development of the disease (Trogstad *et al.*, 2011)**.** Preeclampsia complicating any of a given woman's pregnancies is a significant risk factor for preeclampsia complicating her daughters' pregnancies (Mogren *et al.*, 1999)**.** It was reported that for those women who experienced preeclampsia, the rate of disease was higher in sisters (37%), daughters (26%) and grand-daughters (16%) when compared with daughters-in-law (6%) (Chesley and Cooper, 1986)**.** A large Danish study reported that a history of early- or intermediate-onset preeclampsia in the mother or sister increased the risk of the similar form of preeclampsia by at least 150% compared with an absence of such family histories**.** For those women with a history of late-onset preeclampsia, this risk only increased by 73% (Boyd *et al.*, 2013)**.**

3.7.2. Demographic Factors:

3.7.2.1. Age: Extremes of maternal age have been associated with risk of preeclampsia/eclampsia (Redman and Sargent, 2005). Maternal age ≥40 years has been associated with an increased risk (OR 1.49, 95% CI 1.22–1.82) (Khalil *et al.*, 2013). The WHO Multicountry Survey of Maternal and Newborn Health reported that women ≥35 years were at high risk of preeclampsia, though not eclampsia. However, women ≤19 years of age were at high risk for eclampsia, but not a diagnosis of preeclampsia – probably related to underdiagnosis of preeclampsia in populations of women without full antenatal surveillance (Abalos *et al.*, 2014).

3.7.2.2. Ethnicity: Women belonging to Afro-Caribbean or South Asian ethnicity have been shown to be at higher risk when compared with Caucasians (Wright *et al.*, 2012; Khalil *et al.*, 2013). African-American women with severe preeclampsia demonstrate higher blood pressures and require more antihypertensive treatment, while Caucasian women have a higher incidence of HELLP syndrome (Goodwin and Mercer, 2005).

3.7.3 Past Medical or Obstetric History:

3.7.3.1. Maternal birth weight: Women with low birth weight (<2500 g) have been shown to have double the risk of experiencing preeclampsia (OR 2.3, 95% CI 1.0–5.3) when compared with women who weighed (2500–2999) g at birth (Khalil *et al.*, 2013). Further, the risk increased four-fold for those women who weighed <2500 g at birth and were overweight as adults

(Dempsey *et al.*, 2003). A Danish cohort study reported that there was an increased frequency of preeclampsia in women who were born prematurely and were small-for-gestational age (Rogvi *et al.*, 2012).

3.7.3.2. Stature and pre-pregnancy body mass index (BMI):

Body mass index (BMI) is a measure of body fat based on height and weight. The BMI of preeclamptic patients were estimated based on Equation 4:

$$BMI = \frac{Body\ weight\ (in\ kg)}{Body\ height\ (in\ m)^2} \qquad (4)$$

BMI values (in kg m^{-2}) are categorized as follows (Figure 5):

Underweight = < 18.5 Normal weight = 18.5 – 24.9

Overweight = 25 – 29.9 Obesity = 30 or greater

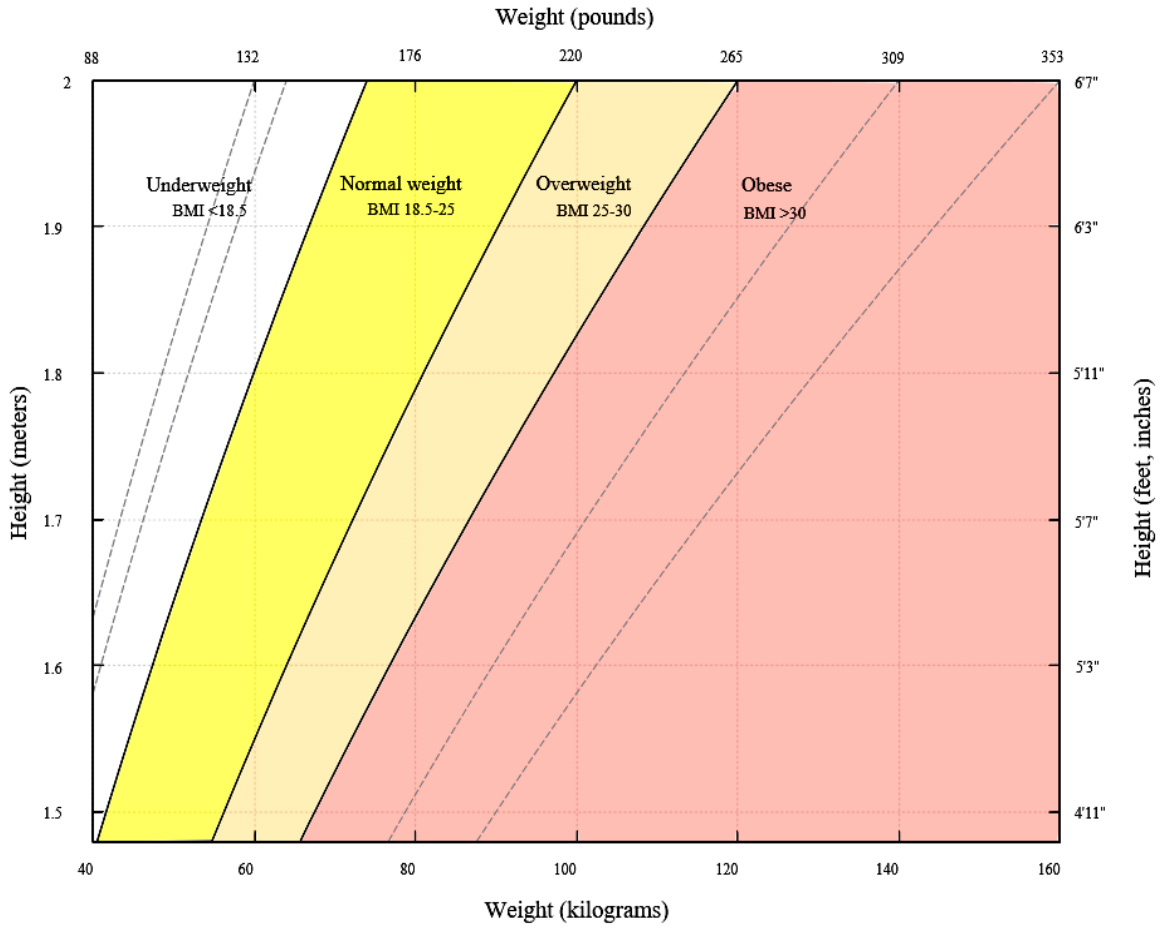


Figure 5. Weight and height wise BMI values (Wikipedia, 2018).

A large population-based study reported that short stature of women (≤164 cm or 5'5") predisposed them to an increased risk of severe preeclampsia (Sohlberg *et al.*, 2011). Women who are overweight or obese are known to be at increased risk for preeclampsia (Shamsi *et al.*, 2013).

3.7.3.3. Pre-existing Medical Conditions: Pre-gestational diabetes (type 1 and type 2) is associated with two- to four-fold increased risk of preeclampsia (Sibai *et al.*, 2000; Feig *et al.*, 2006). It was reported that 23% of women with chronic hypertension were at risk of superimposed preeclampsia (Lecarpentier *et al.*, 2013). The relative risk of superimposed preeclampsia in women with chronic hypertension was nearly eight-fold higher than was preeclampsia in the general pregnancy population (Bramham et al., 2014). Preeclampsia may occur frequently in pregnant women with chronic kidney disease, lupus nephropathy, as well as diabetic nephropathy (Hirose *et al.*, 2014).

3.7.3.4. Parity: Preeclampsia is recognized to more commonly complicate a woman's first pregnancy. A large population-based study reported that nulliparous women were at increased risk of preeclampsia compared with parous women (Odegard *et al.*, 2000).

3.7.3.5. Interval between Pregnancies: The risk of preeclampsia is generally lower in the second pregnancy if conceived with the same partner. In a large cohort study, a birth interval of more than 4 years increased the risk of preeclampsia in women who had no prior history (Mostello *et al.*, 2008).

3.7.3.6. Previous Miscarriages: A Norwegian Mother and Child Cohort study suggested that there might be an increased risk of preeclampsia for women with recurrent miscarriages**.** For women who had recurrent spontaneous abortions and infertility treatment, a three-fold increased risk of preeclampsia was seen compared with controls (Trogstad *et al.*, 2009)**.**

3.7.3.7. Previous Preeclampsia: Women with a history of preeclampsia in a previous pregnancy had an increased risk of preeclampsia in the current pregnancy**.** The risk of recurrent preeclampsia was 12% for those who previously delivered at term and increased to 40% for those who delivered before 28 weeks of gestation (Mostello *et al.*, 2008)**.**

3.7.4. Pregnancy-associated Factors:

3.7.4.1. Multiple Pregnancy: Women with twin pregnancy had higher rates of gestational hypertension and preeclampsia (Sibai *et al.*, 2000)**.** Increased placental mass during a twin gestation may lead to increased circulating levels of soluble fms-like tyrosine kinase-1 (sFlt1), which is a circulating antiangiogenic marker of placental origin, and may play an important role in pathophysiology of, especially early-onset, preeclampsia (Bdolah *et al.*, 2008)**.**

3.7.4.2. Use of Assisted Reproductive Technology: A recent systematic review reported that assisted reproductive technology (ART) (especially *in vitro* fertilization) was associated with higher risk of gestational hypertension and preeclampsia when compared with non-ART pregnancies (Thomopoulos *et al.*, 2013)**.**

3.7.4.3. Infections: Women with a urinary tract infection (UTI) and those with periodontal disease were more likely to develop preeclampsia than women without these infections**.** But there was no association between the other maternal infections such as chlamydia, malaria, treated or untreated HIV and group B streptococcal colonisation and risk of preeclampsia (Conde-Agudelo *et al.*, 2008; Mulla *et al.*, 2015)**.**

3.7.4.4. Congenital Malformations: A large retrospective study from the Perinatal Information System database in Uruguay reported that fetal malformation was associated with an increased risk of preeclampsia (Conde-Agudelo and Belizan, 2000)**.** Congenital anomalies have also been reported to be more strongly associated with early-onset preeclampsia rather than late-onset disease (Lisonkova and Joseph, 2013)**.**

3.7.5. Paternal Factors:

3.7.5.1. Paternal Age: Epidemiological studies suggest that the risk for preeclampsia doubles if the woman has a partner aged >45 years (Chen *et al.*, 2006; Dekker *et al.*, 2011), perhaps as a result of spermatozoa being damaged owing to genetic mutations that occur with ageing or to environmental factors such as exposure to radiation and heat (Shamsi *et al.*, 2013)**.**

3.7.6. Miscellaneous Factors:

3.7.6.1. Smoking: Cigarette smoking is known to have adverse effects on all organ systems**.** But a systematic review of 48 epidemiological studies reported that smoking during pregnancy approximately halves the risk of preeclampsia (England and Zhang, 2007)**.** This protective effect was consistently seen irrespective of parity and severity of disease**.** The pathophysiology of this relationship is not well established**.** However, it is proposed that smoking might have effects on angiogenic factors, endothelial function and the immune system, which may contribute to the lowered risk of preeclampsia (England and Zhang, 2007)**.**

3.7.6.2. Physical Activity: Those women who engaged in high levels of physical activity during pre-pregnancy and continued to do so during early pregnancy, were less likely (by 35% and 21%, respectively) to develop preeclampsia, compared with those who participated in low levels of physical activity (Aune *et al.*, 2014)**.**

3.7.6.3. Mental Health: Depression and anxiety in the first trimester of pregnancy are known to increase the risk of preeclampsia by two- to three-fold (Kurki *et al.*, 2000)**.** In addition, lifetime stress and perceived stress during pregnancy may double the risk of developing preeclampsia; an interaction that may be mediated by the neuropsychoimmunological pathway (Yu *et al.*, 2013)**.**

3.7.6.4. Socioeconomic Status: In developing countries, rural dwellers were twice as likely to develop preeclampsia compared with those living in urban areas**.** Furthermore, women with concurrent anaemia and poor intake of fruits and vegetables were at higher risk of preeclampsia (Endeshaw *et al.*, 2015)**.** Severe anaemia (haemoglobin <70 g/L) was associated with a three-fold greater risk of preeclampsia in women living in less-developed countries (Bilano *et al.*, 2014)**.** A lack of antenatal care and less than secondary-level education were pertinent risk factors for risk of preeclampsia in these regions**.**

3.7.6.5. Micronutrient Deficiencies: Maternal vitamin D deficiency, defined as 25-hydroxy vitamin D <30 nmol/L, was associated with double the risk of preeclampsia when compared with concentrations > 50 nmol/L (Achkar *et al.*, 2014)**.**

3.8 Complications of Preeclampsia

The complications of preeclampsia may include the followings**:**

Fetal growth restriction: Preeclampsia affects the arteries carrying blood to the placenta**.** If the placenta doesn't get enough blood, the baby may receive inadequate blood and oxygen and fewer nutrients**.** This can lead to slow growth known as fetal growth restriction, low birth weight or preterm birth**.**

Preterm birth: If anyone have preeclampsia with severe features, she may need to be delivered early, to save the life of mother and the baby**.** Prematurity can lead to breathing and other problems for baby**.**

Placental abruption: Preeclampsia increases the risk of placental abruption, a condition in which the placenta separates from the inner wall of uterus before delivery**.** Severe abruption can cause heavy bleeding, which can be life-threatening for both the mother and the affected baby**.**

HELLP syndrome: HELLP stands for hemolysis (the destruction of red blood cells), elevated liver enzymes and low platelet count - syndrome is a more severe form of preeclampsia, and can rapidly become life-threatening for both mother and her baby**.** Symptoms of HELLP syndrome include nausea and vomiting, headache, and upper right abdominal pain. HELLP syndrome is particularly dangerous because it represents damage to several organ systems**.** On occasion, it may develop suddenly, even before high blood pressure is detected or it may develop without any symptoms at all**.**

Eclampsia: When preeclampsia isn't controlled, eclampsia - which is essentially preeclampsia plus seizures - can develop**.** It is very difficult to predict which patients will have preeclampsia that is severe enough to result in eclampsia**.** Often, there are no symptoms or warning signs to predict eclampsia**.** Because eclampsia can have serious consequences for both mom and baby, delivery becomes necessary, regardless of how far along the pregnancy is**.**

Other organ damage: Preeclampsia may result in kidney, liver, lung, heart, or eyes, and may cause a stroke or other brain injury**.** The amount of injury to other organs depends on the severity of preeclampsia**.**

Cardiovascular disease: Having preeclampsia may increase the risk of future heart and blood vessel (cardiovascular) disease**.** The risk is even greater if one had preeclampsia more than once or one had a preterm delivery**.** To minimize this risk, after delivery one should try to maintain ideal weight, eat a variety of fruits and vegetables, exercise regularly, and shouldn't smoke**.**

The adverse conditions of preeclampsia are presented in Table 5**.**

Table 5. The adverse conditions of preeclampsia (Magee *et al.*, 2016)**.**

Organ system affected	*Adverse conditionals (that increase the risk of severe complications)*	*Severe complications (that warrant delivery)*
CNS	Headache/visual symptoms	Eclampsia PRES Cortical blindness or retinal detachment Glasgow coma scale <13 Stroke, TIA, or RIND
Cardiorespiratory	Chest pain/dyspnoea Oxygen saturation <97%	Uncontrolled severe hypertension (over a period of 12 h despite use of three antihypertensive agents) Oxygen saturation <90%, need for ≥50% oxygen for >1 h, intubation (other than for Caesarean section), pulmonary oedema Positive inotopic support Myocardial ischaemia or infarction
Haematological	Elevated WBC count Elevated INR or aPTT Low platelet count	Platelet count $<50\times10^9$/L Transfusion of any blood product
Renal	Elevated serum creatinine Elevated serum uric acid	Acute kidney injury (creatinine >150 µM with no prior renal disease) New indication for dialysis
Hepatic	Nausea or vomiting RUQ or epigastric pain Elevated serum AST, ALT, LDH, or bilirubin Low plasma albumin	Hepatic dysfunction (INR >2 in absence of DIC or warfarin/coumarin) Hepatic haematoma or rupture
Feto-placental	Non-reassurring FHR IUGR Oligohydramnios Absent or reversed end-diastolic flow by Doppler velocimetry	Abruption with evidence of maternal or fetal compromise Reverse ductus venosus A wave Stillbirth

AST, aspartate aminotransferase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; FHR, fetal heart rate; INR, international normalised ratio; LDH, lactate dehydrogenase; PRES, posterior reversible leukoencephalopathy syndrome; RIND, reversible neurological deficit <48 h; RUQ, right upper quadrant; TIA, transient ischaemic attack

In summary, the *maternal complications* related to preeclampsia include HELLP syndrome, abruption placenta, cerebral hemorrhage, sepsis/shock, eclampsia, risk of recurrence of preeclampsia in subsequent pregnancies, impaired renal function, impaired liver function, pulmonary edema, maternal death**.** The *fetal complications* from preeclampsia include oligohydramnios, intrauterine death, prematurity, intrauterine growth restriction, intrauterine asphyxia and acidosis, and infant death (Saxena, 2014)**.**

3.9 Predictors of Preeclampsia

According to WHO, a prediction test should be simple, non-invasive, inexpensive, rapid, easy to carry out early in gestation, impose minimal discomfort or risk on the woman, be a widely available technology, and the test results must be valid, reliable and reproducible (Conde-Agudelo *et al.*, 2004; Leslie *et al.*, 2011)**.** The predictors of preeclampsia are discussed below**:**

3.9.1. Clinical Examination:

A) Blood Pressure: Blood pressure, which forms the basis of diagnosis for preeclampsia in all international guidelines, is routinely measured during pregnancy**.** The Society of Obstetrics and Gynaecologists of Canada (SOGC) recommends measurement of blood pressure using a mercury sphygmomanometer, a validated automated blood pressure device or a calibrated aneroid device (Magee *et al.*, 2014)**.** High blood pressure is an indication of the increased vascular resistance observed in preeclampsia**.**

B) **Urine:**

i. Proteinuria: Proteinuria is routinely measured during pregnancy, especially in women with new-onset hypertension occurring after 20 weeks' gestation to establish the diagnosis of preeclampsia (Magee *et al.*, 2014)**.** Underlying renal disease is a recognized clinical risk factor for preeclampsia and as such, documentation of proteinuria early in pregnancy is associated with an increased risk of preeclampsia**.** Recently, significant attention has been devoted to the role of albuminuria, and more specifically for lower levels of albuminuria (or 'microalbuminuria') for the prediction of preeclampsia**.**

A large study (n = 2,486 women) performed at 11^{+0}–13^{+6} weeks demonstrated an increased albumin **:** creatinine ratio in women who later developed preeclampsia compared with those who did not (Poon *et al.*, 2009)**.** Prediction of preeclampsia in early pregnancy (17–20 weeks) by estimating the albumin **:** creatinine ratio was also performed using high-performance liquid chromatography (HPLC) (Baweja *et al.*, 2011)**.** In this cohort of 265 women with singleton pregnancy, six developed preeclampsia; the AUC to predict preeclampsia was 0**.**753**.** Although the interpretation is of a good predictive test, the impact is limited by accessibility to HPLC in clinical practice, especially in less-resourced settings**.**

ii. Podocyturia (podocyte : creatinine ratio): Glomerular epithelial cells (podocytes) are involved in the maintenance of the function and structure of the filtration barrier in the kidney (Kelder *et al.*, 2012)**.** As a consequence of endothelial dysfunction and disruption of the selective filtration barrier in the kidney associated with preeclampsia, these podocytes proteins which

include podocin, nephrin, synaptopodin and podocalyxin, lose their functional ability and are shed in urine (i.e., podocyturia) (Jim *et al.*, 2014; Craici *et al.*, 2013). Podocyturia is expressed as podocytes : creatinine ratio and has been shown to be associated with manifestation of renal dysfunction in women with preeclampsia.

Maternal urine (in early third trimester) mRNA levels of three markers of podocytes (VEGF, nephrin and podocin) using qPCR-based analysis showed that none of the three podocyte markers were strong predictors of preeclampsia independently, but a combination of all the markers showed a moderate performance in predicting the occurrence of preeclampsia (Kelder *et al.*, 2012). Craici *et al.* (2013) examined the predictive accuracy of podocyturia in the second trimester using only podocin as a marker in a prospective cohort study. In contrast to the study by Kelder *et al.* (2012), this study reported 100% sensitivity (95% CI 78–100) and 100% specificity (95% CI 92–100) in predicting preeclampsia, using podocin staining of blood and urine samples.

iii. Calcium (calcium : creatinine ratio): As a result of renal dysfunction (decreasing glomerular filtration rate) which occurs in preeclampsia, there is an increase in serum creatinine and decrease in calcium. Thus a decrease in calcium : creatinine ratio has been reported in some studies (Vahdat *et al.*, 2012). Vahdat *et al.* (2012) studied the predictive accuracy of urine calcium : creatinine ratio of 150 women during late second trimester. Using a cut-off value of 0.071 in this study, calcium : creatinine ratio was a poor predictor for preeclampsia.

3.9.2. Ultrasound Markers:

i. Uterine Artery Doppler Ultrasonography: Doppler ultrasound is a non-invasive technique that can be used to study the uteroplacental circulation and changes in blood flow resistance (Papageorghiou *et al.*, 2002) (Figure 6). The flow change can be measured as pulsatility index (PI) or resistance index (RI) (Bolin *et al.*, 2012; Papageorghiou *et al.*, 2002). As an uncomplicated pregnancy progresses, blood flow resistance in the uterine arteries decreases with gestation owing to invasion of the spiral arteries by the trophoblasts (Lai *et al.*, 2013). The corollary is that increased impedance to blood flow in the uterine arteries has been observed in pregnancies complicated by impaired trophoblast invasion of the spiral arteries, as occurs with placental preeclampsia and IUGR of placental origin (Kleinrouweler *et al.*, 2013).

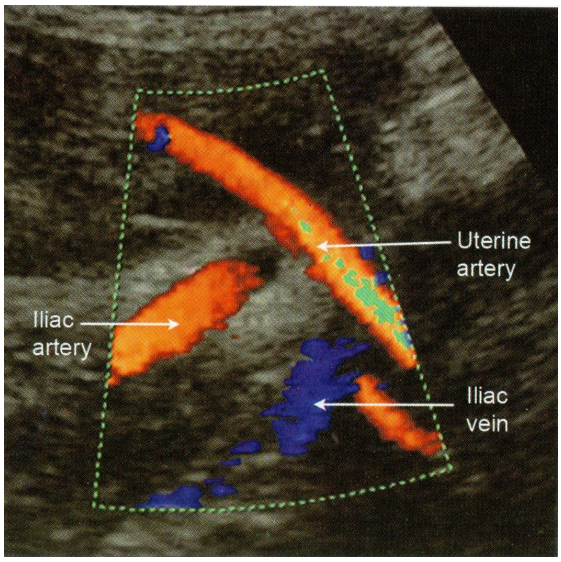


Figure 6. Uterine artery Doppler.

The change in uterine artery blood flow between the first and second trimesters has been examined by screening studies to identify pregnancies at risk of preeclampsia and fetal growth restriction (Bolin *et al.*, 2012). For the prediction of preterm preeclampsia, the AUC ROC of the uterine artery ratio and mean uterine artery difference were 0.701 (95% CI 0.626–0.776) and 0.705 (95% CI 0.599–0.812) respectively. The study concluded that the mean uterine artery difference was the best index for predicting preeclampsia and a better predictor of early-onset preeclampsia.

3.9.3. Laboratory Markers: The markers of preeclampsia risk that become available in the second and third trimesters are based on the pathophysiological changes that characterize preeclampsia and precede clinical disease**.** These include placental perfusion and vascular resistance (e.g., mean second trimester blood pressure, 24-hour ambulatory blood pressure monitoring, Doppler ultrasound); cardiac output and systemic vascular resistance; fetoplacental unit endocrinology (e.g., pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) in the first trimester, and alpha fetoprotein, hCG and inhibin A in the early second trimester); renal function (e.g., serum uric acid or microalbuminuria); endothelial function and endothelial–platelet interaction (e.g., platelet count, antiphospholipid antibodies, or homocysteine); oxidative stress (e.g., serum lipids); and circulating pro- and anti-angiogenic factors (Levine *et al.*, 2004; Lindheimer and Umans, 2006)**.**

3.9.4. Endothelial Dysfunction Tests / Placental Proteins:

i. Fibronectin: Fibronectin, which is released by the placenta, is associated with endothelial damage and inflammation in preeclampsia**.** Higher plasma levels of fibronectin have been reported in women with preeclampsia compared to uncomplicated pregnancies leading to research on its predictive ability for preeclampsia**.** Measurement of total and/or cellular fibronectin in the first or second trimesters had a pooled moderate LR+ and hence may be a useful test for predicting preeclampsia (Leeflang *et al.*, 2007)**.**

3.9.5. Angiogenic Factors:

i. Placental Growth Factor (PlGF): PlGF, which is a member of the vascular endothelial growth factor (VEGF) family, is a pro-angiogenic

factor produced by the syncytiotrophoblast (McElrath *et al.*, 2012; Ghosh *et al.*, 2013). PlGF is at lower maternal circulating concentrations at time of disease with preeclampsia, compared with normal pregnancy. Ghosh *et al.* (2013) evaluated maternal serum PlGF as a predictive test in the second trimester for predicting early-onset preeclampsia and found that PlGF was poorly associated with preeclampsia as a predictive test.

ii. Soluble Fms-like Tyrosine Kinase 1 (sFlt-1): sFlt-1 is an anti-angiogenic factor produced by the placenta. It antagonizes the activities of VEGF and PlGF by binding to them (Villamor and Cnattingius, 2006). This results in reduction of the free circulating levels of VEGF and PlGF, as observed in women with preeclampsia. Compared with PlGF alone or sFlt1 alone, sFlt1 : PlGF ratio gave the best predictive accuracy for preeclampsia and was strongly associated with a positive likelihood of developing preeclampsia.

3.10 Diagnosis of Preeclampsia

The diagnosis of preeclampsia are enlisted in Table 6 (Arias *et al.*, 2008; Daflapurkar, 2014; Saxena, 2014).

Table 6. The diagnosis / investigations of preeclampsia.

Condition	Diagnostic / Investigation Tool	Criteria for Preeclampsia
Physical Examination:		
Elevated Blood Pressure	Roll-over Test with B.P. measurement by mercury sphygmomanometer, a validated automated B.P. device or a calibrated aneroid device at least two occasions four hours apart	≥ 140/90 mm Hg overall; ≥ 20 mm Hg in rolling
Excessive weight gain and Edema	• BMI and Pregnancy weight gain estimation • Puffing hand, face or both • Examination for shortness of breath	• Rapid, large increase in body weight • Edema of hand, face • Pulmonary Edema

continued … …

Condition	Diagnostic / Investigation Tool	Criteria for Preeclampsia
Headache and visual problems	• Mode testing • Examination for changes in vision	• Neurological complication • Temporary loss of vision, blurred vision or light sensitivity
Upper abdominal pain and ankle clonus	• Pain testing under ribs on right side • Clonus and twitching of digits test	• Positive due to liver dysfunction • Positive due to excessive neuro-muscular irritability
Altered Renal Function Examination:		
Proteinuria	• Urinary test	> 300 mg/L or > 1+ on dipstick
Serum creatinine	• Blood test	> 0.8 mg/dL
Uric acid	• Serum uric acid test	> 7 mg/dL
Blood urea Nitrogen	• BUN test	> 15 mg/dL
Altered Liver Function Examination:		
Liver enzymes	• Blood test for liver enzymes (ALT, AST, Bilirubin and GGT) • LDH	Above normal value for each case
Examination of Hematologic Abnormality:		
Hemoglobin and Hematocrit	• Blood hematology test	Increased value for decrease in plasma volume
Platelet count	• Blood thrombocytopenia test	Low platelet count (<150×10^9/L or 150,000/mm^3) due to increased platelet consumption and intravascular destruction (Critical: <50×10^9/L)
Plasma fibrinogen	• Blood hematology test	< 200 mg/dL
Doppler Ultrasound Evaluation:		
Doppler Ultrasound	• Blood velocity waveforms from uterine, umbilical, and middle cerebral arteries by trans-abdominal examination	It can determine hemodynamic repercussion caused by preeclampsia

3.11 Prevention of Preeclampsia

Preventative interventions may be best started before 16 weeks' gestation when most of the physiologic transformation of uterine spiral arteries occurs, or even before pregnancy**.** Such early intervention has the greatest potential to decrease the early forms of preeclampsia that are associated with incomplete transformation of uterine spiral arteries (Ogge *et al.*, 2011)**.** The generally accepted recommendations include the followings**:**

- *Abstention from alcohol*: Reduced consumption of alcohol is recommended to reduce blood pressure in non-pregnant individuals (Khan *et al.*, 2006a), but in pregnancy abstention is recommended as there is no proven safe level of alcohol intake in pregnancy**.**

- *Low-dose Aspirin intake*: There is weak evidence that low-dose aspirin can prevent preeclampsia in moderate-risk women (Duley *et al.*, 2007)**.** But it may be more effective among women at increased risk. It is recommended to initiate low-dose aspirin (75–100 mg/d) at bedtime before 16 weeks of gestation (Magee et al., 2016)**.**

- *High-dose Calcium intake*: There is strong evidence that low-risk women who have low dietary intake of calcium (<600 mg/d) may benefit from calcium supplementation (of at least 1 g/d, orally) to prevent preeclampsia**.** High-risk women are recommended to take calcium supplementation (of at least 1 g/d) if calcium intake is low (Hofmeyr *et al.*, 2014)**.**

- *Dietary changes*: Dietary salt restriction does not affect the incidence of preeclampsia**.** The consumption of milk-based probiotics was associated with a lower risk of preeclampsia in a Norwegian population-based cohort study of 33,399 primiparous women; the decrease was marked for severe preeclampsia (Brantsaeter *et al.*, 2011)**.**

➢ *Lifestyle changes*: Low- to moderate-intensity regular exercise is beneficial for general health, reducing risk of preeclampsia**.** Greater workload and stress have been associated with preeclampsia (Mozurkewich *et al.*, 2000)**.**

➢ *Vitamin D supplementation*: Vitamin D plays a protective role against preeclampsia through beneficial effects on immune modulation and vascular function (Hypponen, 2005)**.** But oxidants such as vitamins C and E does not have effect on preeclampsia**.**

➢ *Micronutrient supplementation*: Magnesium supplementation (of 300 mg/d) prevented an increase in diastolic blood pressure during the last weeks of pregnancy (Bullarbo *et al.*, 2013)**.** Zinc supplementation does not affect preeclampsia**.**

3.12 Management of Preeclampsia

The treatment of preeclampsia is mostly empirical and symptomatic**.** While measures are directed to relieve edema and hypertension, there is no specific therapy for proteinuria which automatically subsides with the control of hypertension**.** The major objectives of management of preeclampsia include the followings**:**

- To stabilize hypertension and to prevent its progression to severe preeclampsia
- To prevent the observed complications
- To prevent preeclampsia
- To deliver a healthy baby in optimal time
- To restore the health of the mother in puerperium

The managements of preeclampsia are directed to mild and severe preeclamptic conditions as well as gestational period**.** Prior to effective management, evaluation of these are important**.** The management of both mild and severe preeclampsia is represented in Figure 7**.**

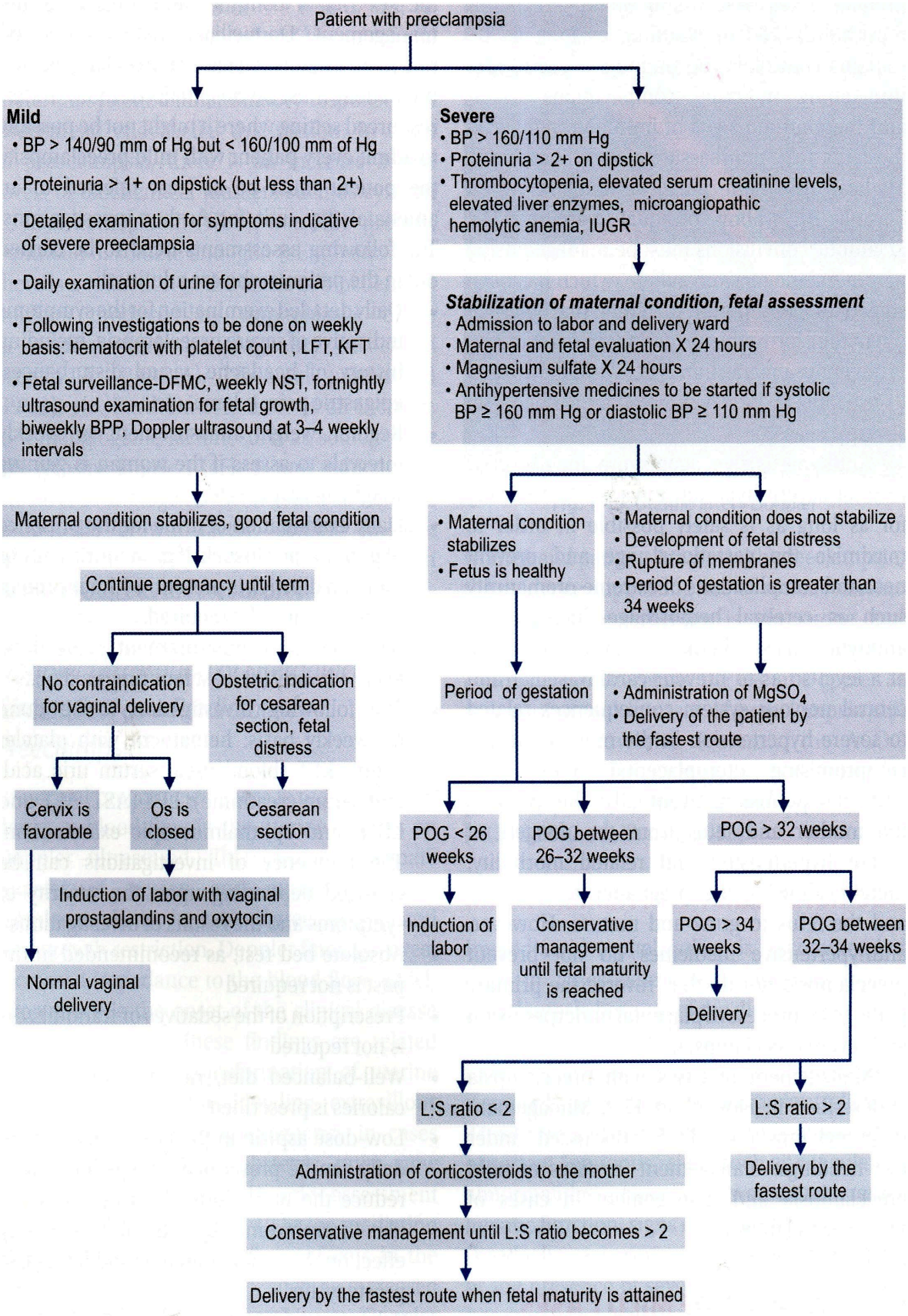


Figure 7. Management of both mild and severe preeclampsia (Saxena, 2014).

For management of preeclamptic patients, the following steps are suggested**:**

1. Assessment on Mild or Severe Preeclampsia: When a hypertensive pregnant woman with complication(s) visited an Obstetrician, she would first evaluate the patient's gestational period (> 37, 32-37 and < 32 weeks)**.** Then based upon patient's B.P. measurement, physical observations (edema of hand and face, vision alteration, upper abdominal pain, ankle clonus and twitching test, shortness of breathing, etc.), past medical and surgical history and clinical investigation reports (proteinuria, serum crreatinine, uric acid, blood hematology test, liver enzyme test, etc.), the obstetrician would confirm the severity of preeclampsia as *Mild or Severe***.** And treatment to be continued accordingly**.**

2. Decision on Hospital or Home Treatment: Ideally, all patients of preeclampsia are to be admitted in the hospital for effective supervision and treatment**.** But in the developing countries, where the prevalence of preeclampsia is more and hospital facilities are limited, uncomplicated mild preeclamptic patients could be under domiciliary treatment**.** In these cases, proper rest, high-protein diet, intake of appropriate drug and prescribed routine investigations are suggested**.**

3. Hospital Management:

i) Rest: Since rest increases uterine blood flow (that improves placental perfusion) and reduces B.P., it is suggested**.** But completed bed rest is not essential**.**

ii) Diet: The diet should contain adequate amount of protein (about 100 g / day)**.** Usual salt intake is permitted. Fluids need not to be restricted. The total calorie should be approximately 1,600 cal / day (Konar, 2016)**.**

iii) Diuretics: The diuretics should not be used injudiciously, as they cause harm to the baby by diminishing placental perfusion and by electrolyte imbalance**.** The compelling reasons for its use are - cardiac failure, pulmonary edema, etc**.** The commonly used diuretic is furosemide (Lasix) 40 mg, given after breakfast for 5 days in a week**.** In acute condition, intravenous route is preferred**.**

iv) Antihypertensives: Antihypertensives drugs (Figure 8) have limited value in controlling B.P. due to preeclampsia**.** The indicators include persistent rise in B.P. especially when diastolic pressure is > 110 mm Hg along with elevated level of proteinuria**.** The common oral drugs employed for the purpose in presented in Table 8 (Figure 7)**.** The drug and dose selections are based upon severity of the complication**.**

Table 7. Some commonly used drugs in the management of preeclampsia (Konar, 2016)**.**

Drug	**Mode of action**	**Dose***
Labetalol	Adrenoceptor antagonist (α and β blockers)	100 mg TID or QID
Nifedipine	Calcium channel blocker	10-20 mg BID
Methyldopa	Central and peripheral antidrenergic action	250-500 mg TID or QID
Hydralazine	Vascular smooth muscle relaxant	10-25 mg BID

* BID, TID and QID correspond to twice/day, three times/day and four times/day respectively**.**

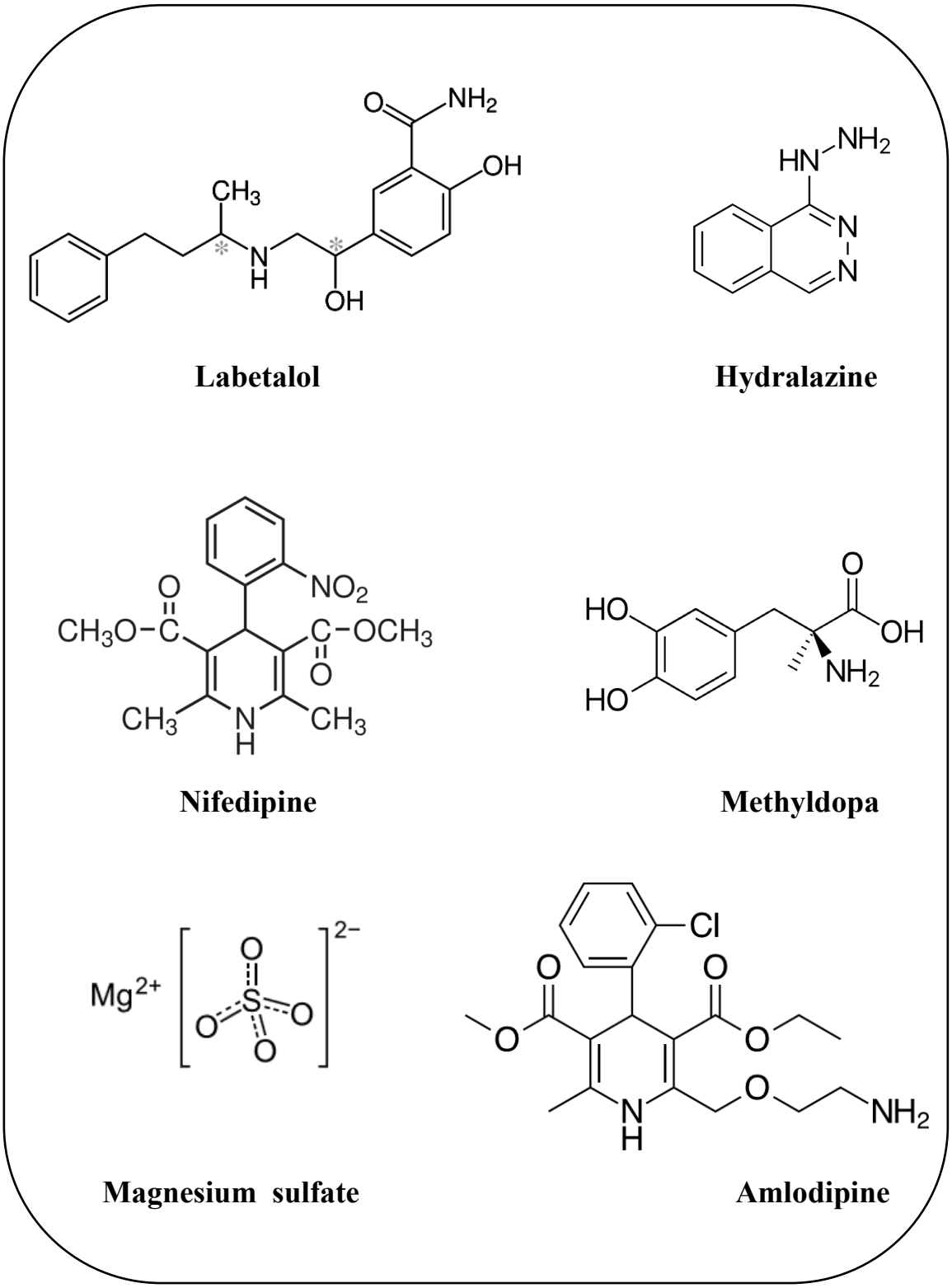


Figure 8. Common drugs used for treatment of preeclamptic patients**.**

4. Monitoring of Maternal and Foetal Conditions:

A) Maternal Monitoring:

1. Measurement of B.P. at least four times per day**.**
2. Measurement of body weight every other day**.**
3. Daily urinary Proteinuria estimation in the first urine voided every morning**.**
4. CBC with Platelet count, LHD, AST, ALT twice per week**.**
5. Physical examinations / questioning on headache, right upper quadrant pain, vision or breathing problem, etc**.**

B) Fetal Monitoring:

1. Fetal biometry every 3 weeks**.**
2. Daily fetal heart rate (FHR) monitoring for 1 hour**.**
3. Daily fetal movement count**.**
4. Umbilical and cerebral Doppler every week**.**

5. Determination of Time and Mode of Delivery:

Delivery (termination of pregnancy) is the only ultimate cure of preeclampsia**.** Its timing and modes or methods are discussed below**:**

A) Timing of Delivery:

1. All women with severe preeclampsia should be delivered within 24 hours, regardless of gestational age**.**

2. For women with non-severe preeclampsia at $<24^{+0}$ weeks' gestation, counseling should include information about delivery within days as an option**.**

3. For women with non-severe preeclampsia at 24^{+0}–33^{+6} weeks' gestation, expectant management should be considered, but only in centers capable of caring for very preterm infants**.**

4. For women with non-severe preeclampsia at 34^{+0}–36^{+6} weeks' gestation, expectant management is advised**.**

5. For women with preeclampsia at ≥37^{+0} weeks' gestation, delivery within 24 hours is recommended**.**

6. For women with non-severe preeclampsia complicated by HELLP syndrome at 24^{+0}–34^{+6} weeks' gestation, consider delaying delivery long enough to administer antenatal corticosteroids for acceleration of fetal pulmonary maturity as long as there is temporary improvement in maternal laboratory testing**.**

B) Mode of Delivery:

1. For women with any hypertensive disorder of pregnancy including preeclampsia, vaginal delivery should be considered unless a Caesarean delivery is required for the usual obstetric indications**.**

2. If vaginal delivery is planned and the cervix is unfavorable, then cervical ripening should be used to increase the chance of a successful vaginal delivery**.** For cervix ripening, prostaglandin (PHE_2) gel 500 μg intracervical or 1-2 mg in the posterior fornix is inserted**.**

3. At a gestational age remote from term, women with a hypertensive disorder of pregnancy with evidence of fetal compromise may benefit from delivery by emergent Caesarean**.**

4. Antihypertensive treatment should be continued throughout labour and delivery to maintain systolic blood pressure at <160 mmHg and diastolic blood pressure at <110 mmHg**.**

5. The third stage of labour should be actively managed with oxytocin 5 units IV or 10 units IM, particularly in the presence of thrombocytopaenia or coagulopathy**.**

6. Ergometrine maleate should not be administered to women with any hypertensive disorder of pregnancy, particularly preeclampsia or gestational hypertension; alternative oxytocics should be considered**.**

6. Continuation of Postpartum Care:

After patient has been delivered, close vigilance must be maintained. After delivery, fluid balance is an important part of management**.** It is often found that antihypertensive therapy can be reduced steadily post-delivery, although occasionally at 24-48 hours there may be need to increase treatment again**.** If drugs are stopped too quickly, rebound hypertension may occur**.** Most women show signs of improvement by 48 hours and will be ready to go home within a few days**.**

3B Prevalence of Preeclampsia

Assessing the epidemiology of preeclampsia is difficult due to lack of conformity of the definitions described above**.** There may also be measurement bias and errors in the ascertainment of both hypertension and proteinuria**.** However, World Health Organization (WHO) from several references estimated the incidence rates for preeclampsia and eclampsia (Table 8; WHO, 2003)**.**

Table 8. Regional incidence rates for preeclampsia and eclampsia(WHO, 2003)**.**

WHO region	WHO area	Preeclampsia incidence rate (% births)	Eclampsia incidence rate (as % preeclampsia)
AFRO D	Algeria, Angola, Benin, Burkina Faso, Cameroon, Cape Verde, Chad, Comoros Equatorial Guinea, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Madagascar, Mali, Mauritania, Mauritius, Niger, Nigeria, Sao Tome and Principe, Senegal, Seychelles, Sierra Leone, Togo	2.8	2.3
AFRO E	Botswana, Burundi, Central African Republic, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Eritrea, Ethiopia, Kenya, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Uganda, United Republic of Tanzania Zambia, Zimbabwe	2.8	2.3
AMRO A	Canada, Cuba, United States of America	0.4	0.8

continued …

WHO region	WHO area	Preeclampsia incidence rate (% births)	Eclampsia incidence rate (as % preeclampsia)
AMRO B	Antigua and Barbuda, Argentina, Bahamas, Barbados, Belize, Brazil, Chile, Colombia, Costa Rica, Dominica, Dominican Republic, El Salvador, Grenada, Guyana, Honduras, Jamaica, Mexico, Panama, Paraguay, Saint Kitts and Newis, Saint Lucia, Saint Vincent and the Grenadines, Suriname, Trinidad and Tobago, Uruguay, Venezuela	2.8	2.3
AMRO D	Bolivia, Ecuador, Guatemala, Haiti, Nicaragua, Peru	2.8	2.3
EMRO B	Bahrain, Cyprus, Iran (Islamic Republic of), Jordan, Kuwait, Lebanon, Libyan Arab Jamahiriya, Oman, Qatar, Saudi Arabia, Syrian Arab Republic, Tunisia, United Arab Emirates	2.8	2.3
EMRO D	Afghanistan, Djibouti, Egypt, Iraq, Morocco, Pakistan, Somalia, Sudan, Yemen	2.8	2.3
EURO A	Andorra, Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland, United Kingdom	0.4	0.8
EURO B	Albania, Armenia, Azerbaijan, Bosnia and Herzegovia, Bulgaria, Georgia, Kyrgyzstan, Poland, Romania, Slovakia, Tajikistan, The Former Yugoslav Republic of Macedonia, Turkey, Turkmenistan, Uzbekistan, Yugoslavia	2.8	2.3
EURO C	Belarus, Estonia, Hungary, Kazakhstan, Latvia, Lithuania, Republic of Moldova, Russian Federation, Ukraine	2.8	2.3
SEARO B	Indonesia, Sri Lanka, Thailand	2.8	2.3
SEARO D	Bangladesh, Bhutan, Democratic People's Republic of Korea, India, Maldives, Myanmar, Nepal, Timor Leste	2.8	2.3
WPRO A	Australia, Brunei Darussalam, Japan, New Zealand, Singapore	0.4	0.8
WPRO B	Cambodia, China, Cook Islands, Fiji, Kiribati, Lao People's Democratic Republic, Malaysia, Marshall Islands, Micronesia (Federated States of), Mongolia, Nauru, Niue, Palau, Papua New Guinea, Philippines, Republic of Korea, Samoa, Solomon Islands, Tonga, Tuvalu, Vanuatu, Viet Nam	2.8	2.3

AFR=Africa; AMR=Americas; EMR=Eastern Mediterranean; EUR=Europe; SEAR=South-East Asia; WPR=Western Pacific; A: very low child, very low adult mortality; B Low child, low adult mortality; C: Low child, high adult mortality; D: High child, high adult mortality; E: High child, very high adult mortality

The most commonly cited and accepted estimate of hypertensive disorder of pregnancy occurrence is 5–10% (Cunningham et al., 2009). This is valid for high-income countries (HICs) in several large national cohorts that have reported rates of 4.6–9.2% based on publications since 1995 (Hayes *et al.*, 2014; Morikawa *et al.*, 2014; Verburg *et al.*, 2015). Chronic hypertension and gestational hypertension appear to be much less common than preeclampsia, although limited population-level estimates exist.

Chronic hypertension (≈ 1%)

WHO conducted Multicountry Survey on maternal and newborn health, in which 313,030 women were admitted to 357 health facilities in 29 countries across Africa, Asia, Latin America and the Middle East during 2010 to 2012 (Abalos *et al.*, 2014). Reliable estimates for low- and middle-income countries (LMICs) settings for chronic hypertension, based on the survey, found a prevalence of 0.3% in the total cohort. More reliable estimates are available for high-income countries (HICs). In a national cohort of all hospital deliveries in Canada in all provinces except Quebec (2003–2010), the incidence of chronic hypertension was 0.4%, in which 0.6% in Alberta (Nerenberg *et al.*, 2013; Mehrabadi *et al.*, 2014). In the American National Inpatient Sample data set, chronic hypertension complicated 1.5% of births (2007–2008) (Bateman *et al.*, 2012). A similar rate of 1.3% was reported in the UK (1996–2010) (Liu *et al.*, 2015).

Gestational hypertension (≈ 3%)

Very limited data on prevalence of gestational hypertension for LMICs and no data giving a reliable estimate of the incidence was obtained**.** In a hospital-based cohort of 193,554 births registered in two provinces of Southern China (1993–1996), gestational hypertension occurred at a rate of 9**.**5% (Li *et al.*, 2013); this was a secondary analysis of data from a study evaluating the impact of folic acid supplementation on the incidence of neural tube defects and there is likely to be selection bias**.** Gestational hypertension rates in HICs differ substantially from those described above**.** In a national cohort of all hospital deliveries in Canada in all provinces except Quebec (2003–2010), the incidence of gestational hypertension was 1**.**1% (Mehrabadi *et al.*, 2014)**.** In New York State, USA (1995–2004), gestational hypertension complicated 1**.**4–2**.**5% of births (2007–2008) (Bateman *et al.*, 2012)**.**

Preeclampsia (≈ 2–4%)

In the largest hospital-based cohort to report prevalence of pre-eclampsia in LMICs, the WHO Multicountry Survey reported an overall prevalence of 2**.**2% ranging from 1**.**4% in the Middle East region to 3**.**9% in the African region (Abalos *et al.*, 2014)**.** Other cohorts reviewed since 1995 reported prevalence estimates ranging from 1**.**2% to 8**.**4%16–19**.** In a WHO systematic review of 129 studies covering approximately 39 million women from 40 countries (2002–2010), the crude incidence of preeclampsia was

2.3% (4.6% using a model-based estimate to account for lack of data sets from certain regions causing under-representation of countries believed to have higher rates of preeclampsia), ranging from 1.2% in the Middle East to 4.2% in the Western Pacific (Abalos *et al.*, 2013). However, there was substantial regional variation, from 0.7% reported in a small study from Morocco to 15.6% reported in a Turkish data set. If estimates are restricted to those from national cohorts, data were available from seven countries that collectively reported preeclampsia rates of 1.4–4.0% (Abalos *et al.*, 2013).

HELLP syndrome (< 1%)

There are few epidemiological data about the prevalence of HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome, a severe manifestation of preeclampsia. A 2009 review of management of HELLP syndrome quotes a prevalence of 0.5–0.9% of all pregnancies, based on small case series and retrospective hospital- and USA-based cohort studies published in the early 1990s (Haram *et al.*, 2009). A more recent, but small, retrospective hospital-based cohort included 5,155 women admitted to a tertiary academic centre in Turkey (1997–2004) and found an incidence of HELLP of 0.5% (Yucesoy *et al.*, 2005). Other LMIC- and HIC-based cohort studies suggest a higher prevalence of HELLP syndrome ranging from 2.5% to 50% (Rachdi *et al.*, 1993; Williams and Wilson, 2002; von Dadelszen *et al.*, 2011). However, some of these studies are tertiary facility-based with cohorts of women selected based on complicated preeclampsia.

3C Some Recent Studies on Hypertension and Preeclampsia

Adu-Bonsaffoh *et al.* (2017) performed a cross-sectional study on the prevalence of various categories of hypertensive disorders in pregnancy (HDP) in Korle Bu Teaching Hospital (KBTH) of Ghana. There were a total of 398 women with HDP among 1,856 deliveries during one year resulting in prevalence of 21.4%. The proportions of the various types of HDP included 184 (50.0%), 140 (38.0%), 23 (6.3%) and 21 (5.7%) representing gestational hypertension, preeclampsia, chronic hypertension and superimposed preeclampsia respectively (Figure 9). Eclampsia occurred in 58 (15.8%) women.

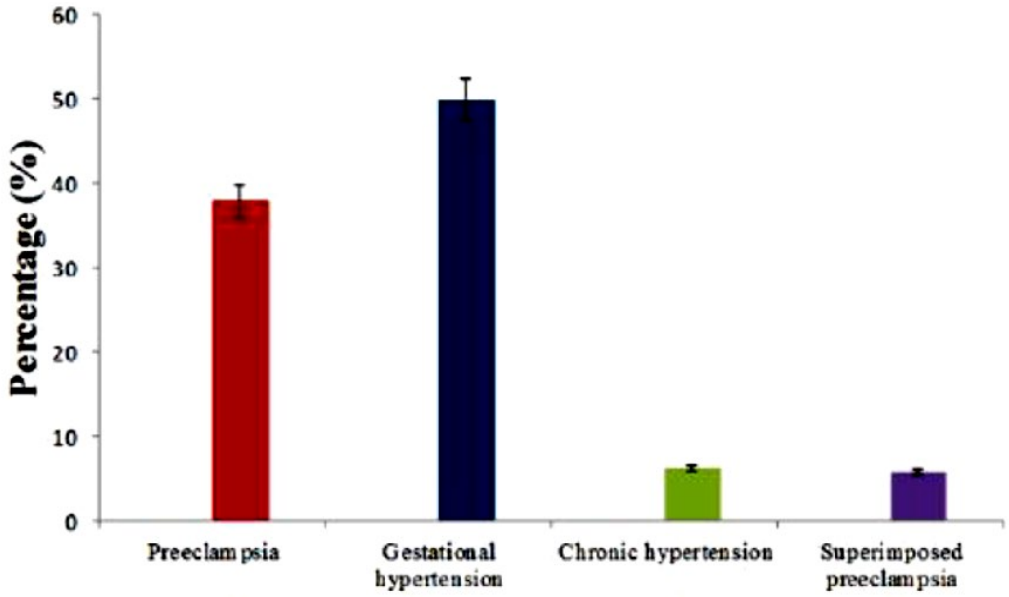


Figure 9. Frequency of the various types of hypertensive disorder in pregnancy at KBTH, Ghana.

Chun Ye *et al.* (2014) conducted a multicenter cross-sectional retrospective study to estimate the prevalence and analyze the risk factors for HDP among the pregnant women who had referred for delivery in 2011 in China Mainland. A total of 112,386 pregnant women were investigated from 38 secondary and tertiary specialized or general hospitals, of which 5,869 had HDP, accounting for 5.22% of all pregnancies. There were significant differences in the prevalence of HDP between geographical regions, in which the North China showed the highest (7.44%) and Central China showed the lowest (1.23%). Of six subtypes of HDP, severe preeclampsia accounted for 39.96%, gestational hypertension for 31.40%, mild preeclampsia for 15.13%, chronic hypertension in pregnancy for 6.00%, preeclampsia superimposed on chronic hypertension for 3.68% and eclampsia for 0.89%.

They (Chun Ye *et al.*, 2014) identified a number of risk factors of HDP including twin pregnancy, age of >35 years, overweight and obesity, primipara, history of hypertension as well as family history of hypertension and diabetes. The prevalence of pre-term birth, placental abruption and postpartum hemorrhage were significantly higher in women with HDP than those without HDP. Their summarized findings are represented in Table 9.

Table 9. Differences in pregnancy and perinatal outcomes between women with and without HDP in China (Chun Ye *et al.*, 2014).

A) Differences in Pregnancy Outcomes:

Group	N	Preterm Birth (%)	Placental Abruption (%)	Postpartum Hemorrhage (%)	Cesarean Section (%)
GH	2016	227(11.26)	16(0.79)	143(7.09)	1327(65.82)
Mild Preeclampsia	888	128(14.41)	19(2.14)	58(6.53)	695(78.27)
Severe Preeclampsia	2345	1166(49.72)	129(5.50)	132(5.63)	2023(86.27)
Eclampsia	52	37 (71.15)	6(11.54)	1(1.92)	49(94.23)
PSCH	216	113(52.31)	14(6.48)	13(6.02)	176(81.48)
CHP	352	52(14.77)	4(1.14)	31(8.81)	246(69.89)
With HDP	5869	1723(29.36)	188(3.20)	378(6.44)	4516(76.95)
Without HDP	106517	7226(6.78)	452(0.42)	3821(3.59)	56834(53.36)
Total	112386	8949(7.96)	640(0.57)	4199(3.74)	61350(54.59)
X2		3867.7	758.6	125.9	1248.698
P		<0.001	<0.001	<0.001	<0.001

B) Differences in Perinatal Outcomes:

Group	N	LBW (%)	Neonatal Asphyxia (%)	Perinatal Death (%)
GH	2091	214(10.23)	102(4.88)	44(2.10)
Mild Preeclampsia	949	159(16.75)	58(6.11)	11(1.16)
Severe Preeclampsia	2522	1134(44.96)	479(18.99)	206(8.17)
Eclampsia	53	40(75.47)	24(45.28)	5(9.43)
PSCH	222	93(41.89)	66(29.73)	31(13.96)
CHP	358	40(11.17)	31(8.66)	17(4.75)
With HDP	6195	1697(27.39)	760(12.27)	314(5.07)
Without HDP	108192	6167(5.70)	3689(3.41)	1456(1.35)
Total	114387	7864(6.87)	4449(3.89)	1770(1.55)
X2		4306.9	1230.0	533.1
P		<0.001	<0.001	<0.001

In Iran, the occurrence of hypertensive disorders in pregnancy (HDP) is considerably low compared to the global values. Zibaeenezhad *et al.* (2010) found 563 pregnant women out of 24,196 as hypertensive which is 2.32% [comparable to the data of USA, 3.8% (NHLBI, 2000)]. The prevalence of chronic hypertension, preeclampsia and eclampsia were 2.13%, 0.17%, 0.03% respectively. Thus preeclampsia represented 84–94%

of HDP (Figure 10). It was found that 45.8% of all patients with hypertension disorders of pregnancy experienced caesarian section method of delivery.

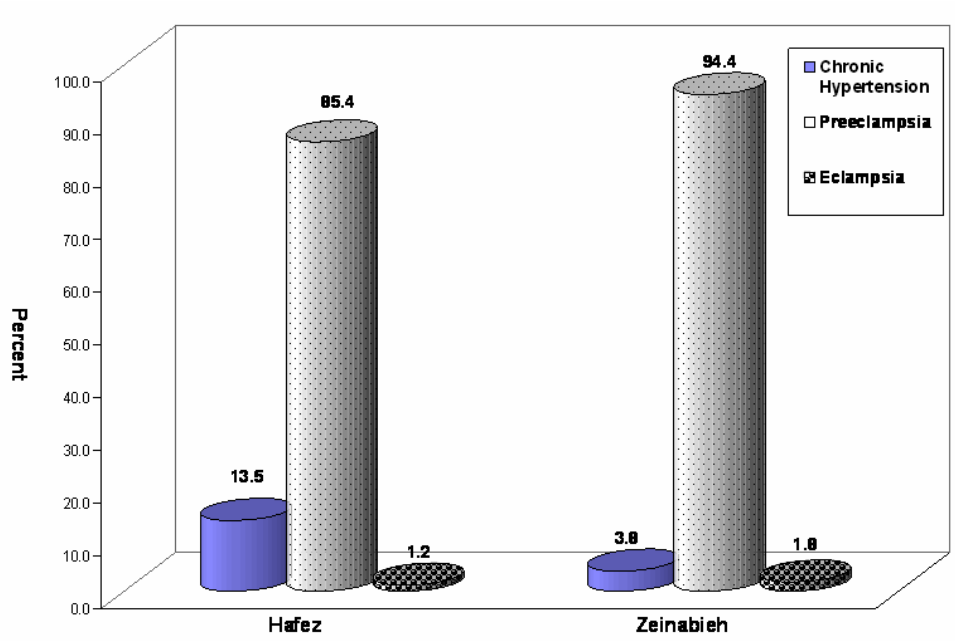


Figure 10. The prevalence of 3 types of hypertensive disorders of pregnancy in Hafez and Zeinabieh hospitals of Iran (Zibaeenezhad *et al.*, 2010).

Prompt diagnosis using an accurate and quick laboratory test results in a decrease in maternal mortalities caused by pregnancy induced hypertension. Flores and Pelaez-Crisologo (2009) performed a cross-sectional study to correlate 4-hour, 8-hour and 12-hour urine protein values with the 24-hour urine protein value in women of Philippines with HDP. For this, a linear regression model was run using the data and the coefficient of determination (r^2) was 94% ($p<0.001$). The linear model was found to be

$$TP24 = -2.51(TP4) + 4.45(TP8) + 0(TV12) + 0(TV24)$$
$$+ 0.31(age) - 0.375(score\ 3)$$

Here TP24, TP4, TP8 is the total protein in a 24, 4, and 8 hour collections, respectively. While TV12 and TV24 represent the total volume of the 12 and 24 hour collection correspondingly and age refers to the patient's age and score 3 indicates the number of miscarriages that the patient has had. Simplification of the model led to

$$TP24 = -251\ (TP4) + 4.45\ (TP8)$$

Only the 4- and the 8-hour samples were found to be statistically significant variables associated with the 24 hour sample. Cut-off values for the 8-hour sample were determined to be <100 mg for no proteinuria and >657 mg for severe proteinuria. This reflects that 8-hour collection is an acceptable alternative to the 24-hour gold standard resulting to more rapid diagnosis and a more accurate one to shortened time to delivery that would lead to decreased perinatal morbidity.

Hladunewich *et al.* (2007) suggested that preeclampsia is a two-stage disease. The first stage is asymptomatic, characterized by abnormal placental development during the first trimester resulting in placental insufficiency and the release of excessive amounts of placental materials into the maternal circulation. This in turn leads to the second, symptomatic stage, wherein the pregnant woman develops characteristic hypertension, renal impairment,

and proteinuria and is at risk for the HELLP syndrome, eclampsia, and other endorgan damage**.** Pathologic examination of placentas from preeclamptic pregnancies generally reveals placental infarcts and sclerotic narrowing of arteries and arterioles, with characteristic diminished endovascular invasion by cytotrophoblasts and inadequate remodeling of the uterine spiral arterioles**.**

Salama *et al.* (2015) evaluated histological changes of placental villi and blood vessels in pregnancy complicated by preeclampsia**.** The placentas showed aggregation of syncytiotrophoblast cells, hyaline degeneration of connective tissue core, and endothelial lining of stem blood vessel; villous core was devoid of fetal blood vessel**.** Diffuse fibrous tissue formation, hypertrophic musculosa of stem blood vessel up to endarteritis obliterans and placental tissue bridges crossing intervillous spaces and villous arborization formed only of connective tissue with no cellular elements were observed**.** Electron microscopy confirmed these findings and showed attenuated blood vessels and excessive villous arborization covered with fibrin-like material (Figure 11)**.**

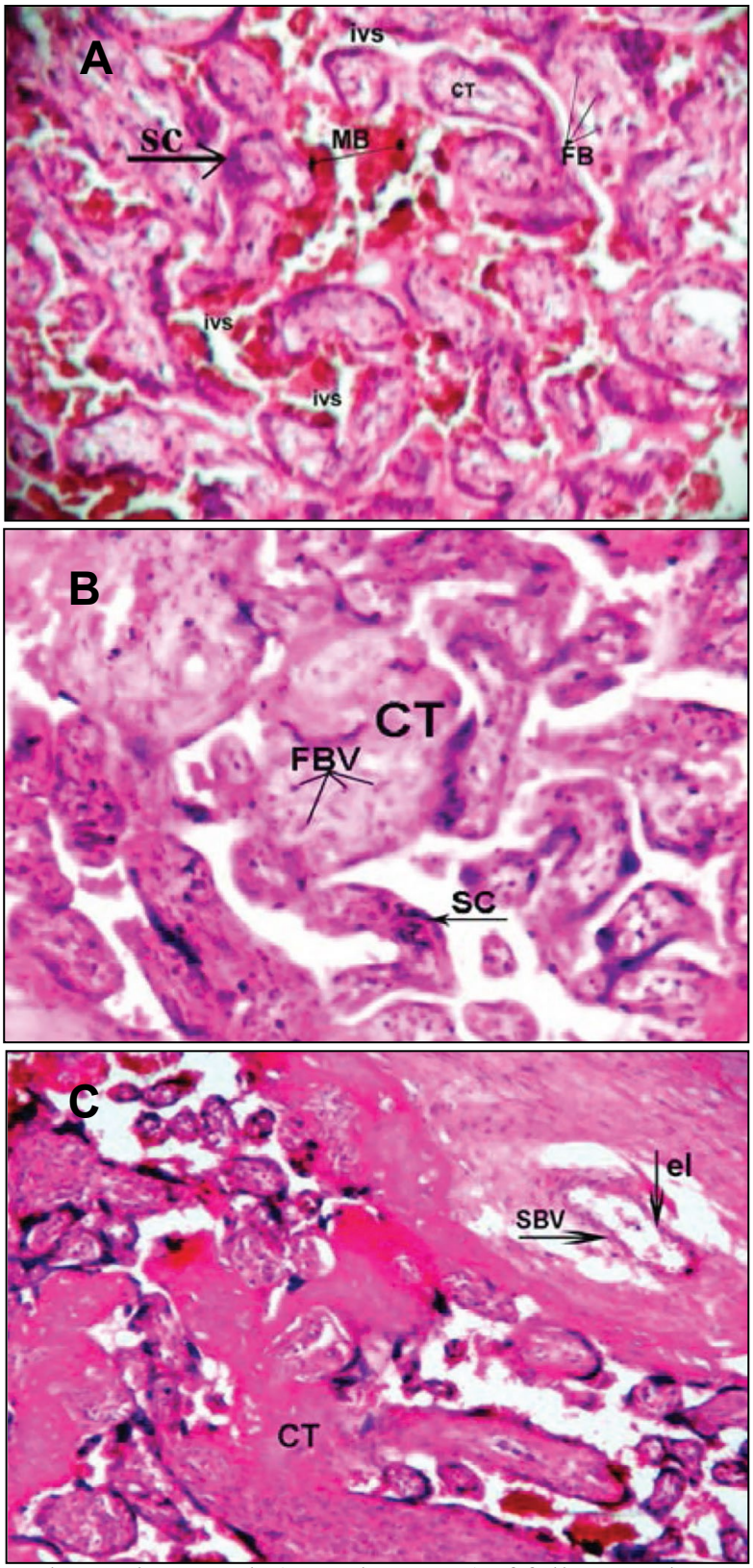


Figure 11. A photomicrograph (H and E ×250)of full-term placenta in a woman**.** [*A (Normal)*: Villi covered with syncytiotrophoblastic cells (SCs) and contained

connective tissue core (CT) with normal fetal blood vessels (FB). The intervillous spaces (IVS) are filled with maternal blood (MB). *B (Mild Preeclampsia)*: Villi covered with syncytiotrophoblast (SCs) and a connective tissue core (CT) enriched with fetal blood vessels. *C (Severe Preeclampsia)*: aggregation of syncytiotrophoblast cells (SCs), hyaline degeneration of connective tissue core (CT), and degeneration of endothelial lining (el) of stem blood vessel (SBV).]

Turner *et al.* (2007) found that in Australia aneroid sphygmomanometers provided more accurate results than mercury sphygmomanometers. But Anderson *et al.* (2010) found that mercury sphygmomanometers gave better result than aneroid one. Jorge Emmanuel of UNDP (2013) provided guidance on calibrating clinical sphygmomanometers. For a test device to pass, its mean error ($\bar{x}_n$) of paired blood pressure determinations of the systolic and diastolic blood pressures for all subjects (Equation 2) should be ≤5 mm Hg.

$$\bar{x}_n = \frac{1}{n}\sum_{i=1}^{n}(P_{ti} - P_{ri}) \qquad (2)$$

where, $\bar{x}_n$ is the mean error over all subjects, P_{ti} is the blood pressure reading of the test device, P_{ri} is the blood pressure reading of the reference sphygmomanometer, and n is the number of determinations. Alternatively, The standard deviation SD_n of the mean error for all subjects is given by:

$$SD_n = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x}_n)^2} \qquad (3)$$

where, $x_i = (P_{ti} - P_{ri})$ of a paired blood pressure determination (i.e., paired determination using the test device and the reference sphygmomanometer).

If the standard deviation SD_n be ≤ 8 mm Hg, then the devised would be passed (UNDP, 2013).

CHAPTER FOUR :

MATERIALS AND METHODS

This section comprises materials, instrumentation, study area, respondent selection, questionnaire development, patient screening techniques, methods of bio-clinical investigations, data collection, quality control and statistical analysis. Each part of the section is represented below elaborately.

4.1 Materials

The reagents are of high purity Analytical Reagent (A.R.) grade and used without further purification. The reagents involved in serum creatinine test involved 17.5 mmol/L picric acid ($C_6H_3N_3O_7$), 0.29 mol/L NaOH and 2 mg/dL Creatinine ($C_4H_7N_3O$) aqueous standard solution (SPINREACT, Spain). For urinary albumin test, high purity reagents of Esbach's Albuminometer and 5% (v/v) acetic acid were employed. Two types of diluting fluids were utilized in the investigation (Khaleque and Mamun, 2011; SPINREACT, 2017). *R.B.C. Diluting Fluid* was prepared by mixing 99.0 mL of 3% (w/v) aqueous sodium citrate, $Na_3C_6H_5O_7$ (Merck, Germany) and 1.0 mL of neutral formalin. *Platelet Diluting Fluid* was prepared as before in which 2 drops of 1% brilliant cresyl blue in saline was added in addition. It is to be noted that sterilized and double distilled de-ionized water (DDW) was used throughout.

4.2 Instrumentation

The main instruments used in the investigation were Research Motorized Inverted System Microscope (Fluorescence Illuminating), UV-VIS Spectrophotometer and Sphygmomanometer (both Mercury and Aneroid). It is to be noted that some other sophisticated instruments were also employed to estimate the clinical parameters and are not discussed here. The details of the instruments are illustrated below:

A) Fluorescence Illuminating Motorized Inverted System Microscope: The components of IX71 Research Inverter System Microscope (Fluorescence Illuminating) employed in the present investigation (OLYMPUS Corporation, Japan) are shown below.

Figure 12. Components of Fluorescence Illuminating Motorized Inverted System Microscope.

In IX71, the UIS2 optics are designed to maximize S/N ratio and optical performance for live cell fluorescence imaging**.** The UIS2 objective lenses have been designed to maximize signal to noise and outperform existing objectives by as much as 50%**.** New objective characteristics include carefully selected low autofluorescence glass (with a significant reduction of fluorescence emitted by the antireflection coating and bonding material), combined with increased signal brightness to improved numerical apertures (N.A.)**.** With even faint fluorescence efficiently detected under weak excitation light, the UIS2 system sets new standards for fluorescence imaging of live cells**.**

The two objectives for use with the UIS2 system are the PLAPON60XO, whose N.A. level of 1**.**42 is the best available for fluorescence imaging, and the UPLSAPO100XO, which is suitable for all applications**.** In addition to their high fluorescence S/N ratio, both these lenses are able to handle UV excitation light at parfocal 45 mm**.** The UPLSAPO100XO provides a transmittance of up to 340 nm**.**

Figure 13. High numerical apertures (N.A.) objectives for fluorescence imaging**.**

The Instrument's high transmittance from visible to near-infrared light is due to its UW multi-coating which effectively cuts reflection over the super wide band spectrum**.** The highest class UIS2 objectives are the UPLSAPO series, whose super apochromatic features effectively compensate for chromatic aberration from the visible spectrum all the way to 1000 nm**.** The optical path of IX71 is shown in Figure 14**.**

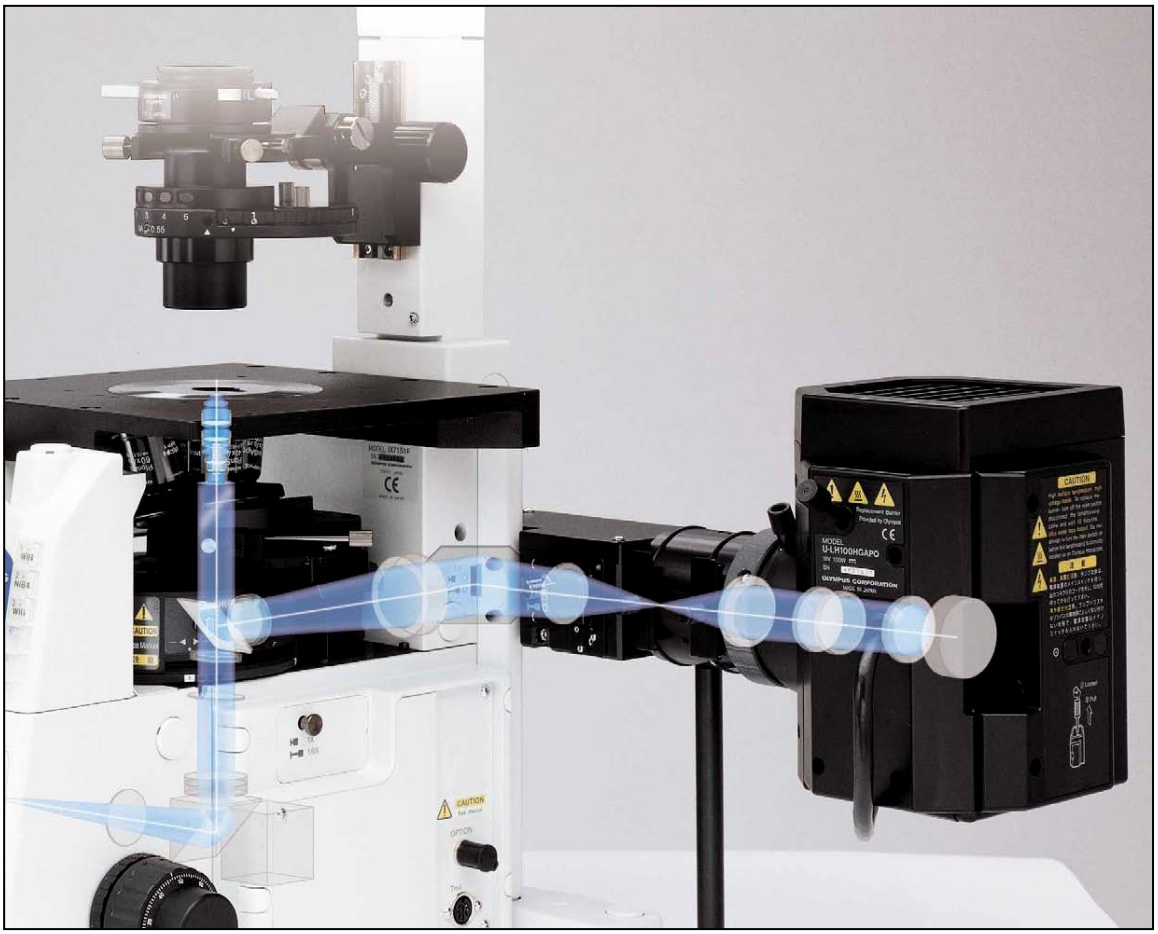


Figure 14. The optical path of IX71 motorized inverted system microscope**.**

B) UV-VIS Spectrophotometer: The UV-VIS spectrophotometer used in the colorimetric analysis was DR/4000 U (HACH Company, Colorado, USA)**.** It was a microprocessor controlled, single-beam spectrophotometer and consisted of i) Light sources, ii) Monochromator, iii) Detector and iv) Display system**.**

Two types of continuous light sources were used in DR/4000 U spectrophotometer**:** tungsten/halogen lamp and deuterium lamp (HACH, 2000)**.** The tungsten/halogen lamp is useful for the wavelength region between 240 and 2500 nm, and deuterium lamp between 160 and 380 nm**.** In the present investigation, the tungsten/halogen lamp was used**.**

The optical system (Figure 15), used in the present experiment, is composed of a split-beam diffraction grating Seya-Namoika monochromator. The monochromator provides a full 190 to 1100 nm wavelength range with a nominal bandwidth of 4 nm, wavelength accuracy ± 1 nm and resolution ± 0.1 nm. The detector system comprises a photomultiplier tube (PMT) and an electrical signal processor. The DR/4000 U provides results in operator-selectable readout modes of Absorbance (ABS), Percent Transmittance (%T) or Concentration. Its dynamic range is -3.0 to 3.0 A with photometric linearity of ± 0.002 A. The instrument also provides for storage of up to 200 user-generated calibrations. Data can be transferred from DR/4000 U to computer using HachLink™ software as Excel spreadsheet. It also accommodates various sample cells of different sizes, but stray light is <1%.

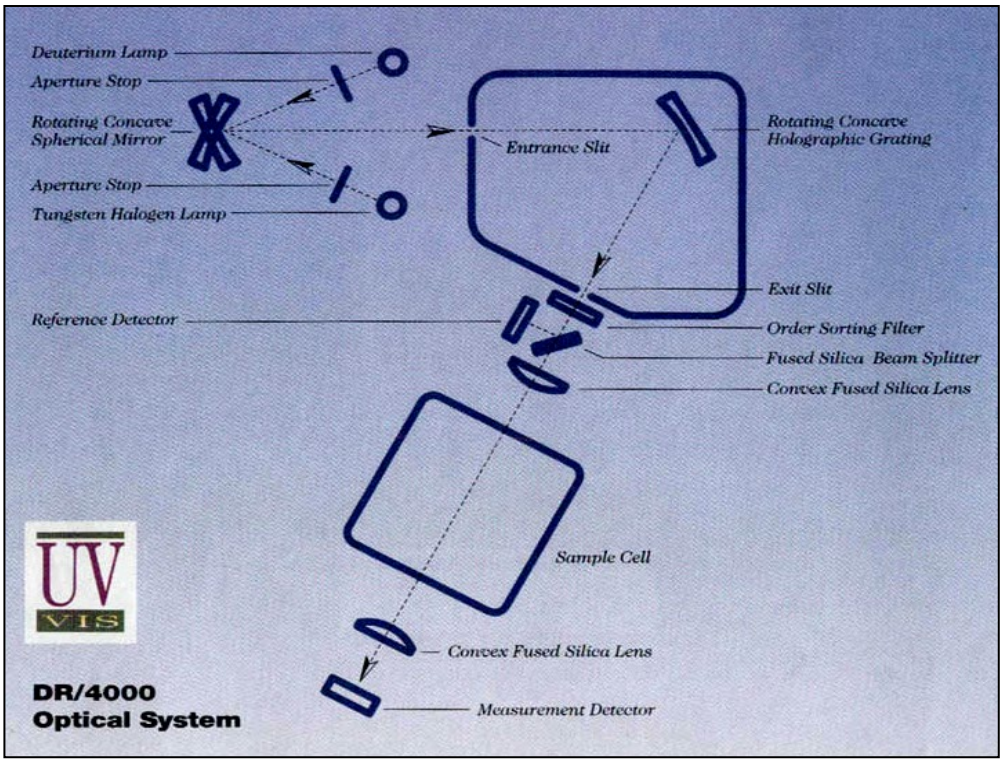


Figure 15. Optical system of DR/4000 U UV-VIS spectrophotometer.

C) Sphygmomanometer: Since for preeclamtic patients' blood pressure (B.P.) is of serious concern, two types of sphygmomanometers - Mercury and Aneroid (Figure 16)- were employed for the purpose**.** High precision *Nova-presameter® mercury sphygmomanometer* (Riester, Jungingen, Germany) was employed to monitor patients' B.P**.** It contained 99**.**99% pure Hg, latex bulb with chromium plated release valve, precision air release valve with fine regulation**.** The instrument could be read up to 300 mm of Hg, with maximum error tolerance of +/- 3 mm of Hg**.** The FDA approved SP-110 *Santadical® Aneroid Sphygmomanometer* (SantaMedcal, Los Angeles, USA) was also employed to monitor patients' B.P**.** It was properly calibrated and featured that of Hg, except for replacing column by gauge**.**

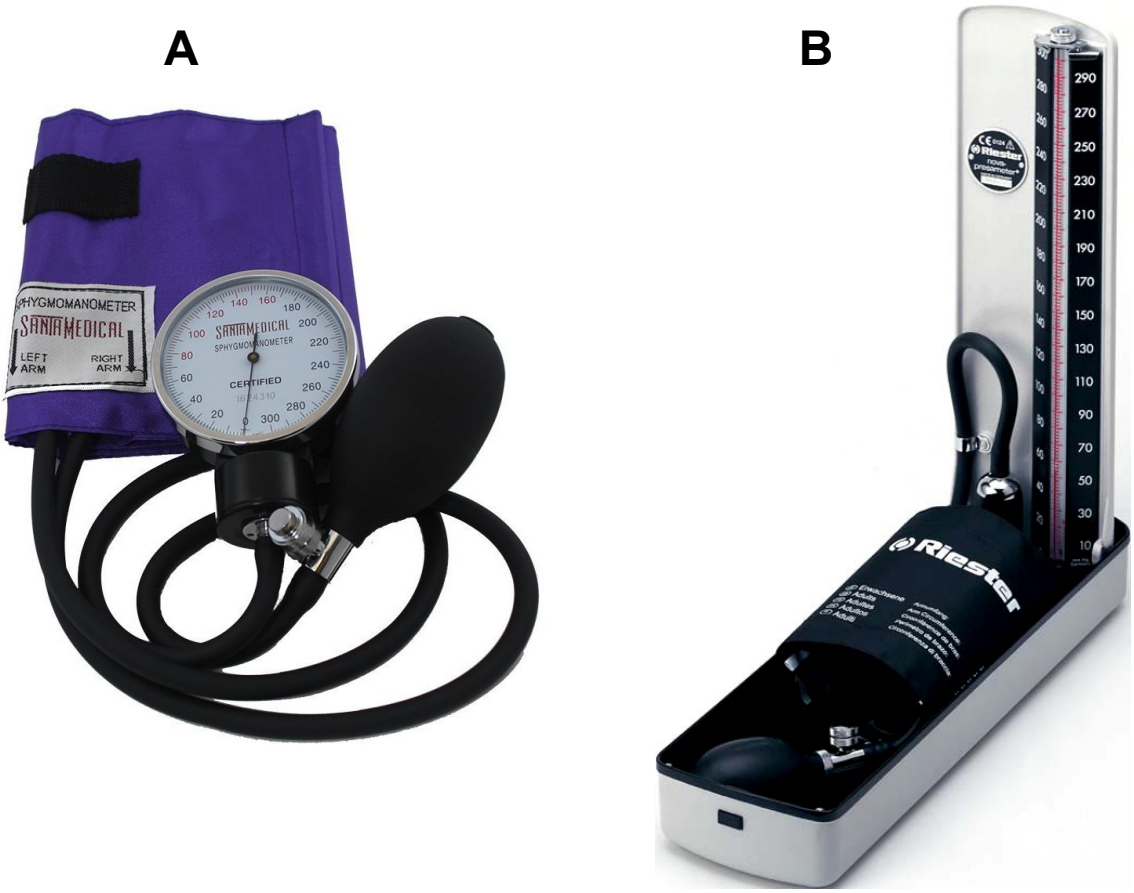


Figure 16. Sphygmomanometers used in the study. [A: Aneroid, B: Mercury]

The 3M^{TM} Littmann® Master Classic II Stethoscope (New York, USA) was employed to complete B.P. monitoring**.**

4.3 Study Area

The study was performed in Rajshahi, the north-western district of Bangladesh. The geographical coordinates of the study area were 24°28'07.29" N to 24°22'16.51" N and 88°19'29.96" E to 88°36'30.69" E, that comprised an area of about 340.32 km^2 (Figure 17). The study area was under four Upazillas or Thanas, namely, Boalia, Shamukhdum, Rajpara and Godagari. The seven concerned hospitals and clinics where the preeclamptic patients were attended and data were recorded are represented in Figure 3. The details are provided in Respondent Selection section. It is to be noted that among the hospitals and clinics, Rajshahi Medical College Hospital - the tertiary referral medical hospital, was the key for the investigation.

Figure 17. Study area for the investigation. [● represents study hospital or clinic]

4.4 Respondent Selection

The female pregnant women visiting ODP or admitted into the following seven hospitals and clinics, and after screening considered as "Preeclamtic Patients" are treated as respondents in this investigations**.** The concerned seven hospitals and clinics are presented in Table 10**.**

Table 10. Hospitals and clinics for preeclamtic study**.**

Sl No.	Hospital or Clinic Name	Location Address	Patients Attended	
			Number	Percent
1	Rajshahi Medical College Hospital (RMCH)	Town: Laxmipur Thana: Rajpara	60	66.67
2	Motherland Hospital	Town: Laxmipur Thana: Rajpara	05	5.56
3	Islami Bank Hospital	Town: Laxmipur Thana: Rajpara	08	8.89
4	Janaseba Clinic	Town: Upashohor Thana: Boalia	03	3.33
5	Islami Bank Medical College Hospital	Town: Nawdapara Thana: Shahmukhdum	05	5.56
6	Godagari General Hospital	Village: Daingpara Thana: Godagari	05	5.56
7	Godagari Model Hospital	Village: Daingpara Thana: Godagari	04	4.44
		Total	**90**	**100.00**

A total of 90 preeclamptic patients of age 16 - 38 were the respondents of this study**.** The respondents are not only from Rajshahi districts, but also from other neighboring districts, as Rajshahi Medical College Hospital (RMCH) is a tertiary referral hospital**.** In fact, in winter (the peak time for preeclamtic patients) RMCH sometimes cannot accommodate all the patients**.** In the study, two-thirds of the preeclamtic patients were of this hospital**.**

4.5 Questionnaire Development

For keeping records and analyses, a multi-level 6 page questionnaire with annexes was developed **(Appendix 1).** It contains - 1) Demographic Information, 2) Food Habit, 3) Environmental Impact Study, 4) Gynecological and Obstetrical History, 5) Past Medical and Family History, 6) Stress Estimation, 7) Physiological and Clinical Profile, 8) Confirmation and Follow up, and 9) Outcome**.** Some parameters such as Body Mass Index, Socioeconomic Index and Stress Index (**Appendix 4**) were estimated from online, based on the acquired data**.**

At the beginning of the interview **(Appendix 9)**, the purpose of the study was told to the patient clearly**.** After being agreed for cooperation, her consent were recorded in written in "Consent Form" (**Appendix 1**)**.** The *Demographic Information* page contained age, weight and height from which **Body Mass Index (BMI)** was estimated from online (NIH, 2018)**.** It also contained ethnicity, religion, education, occupation, income level, wealth, living situation, from which **Socioeconomic Index** was estimated from online (The New York Times, 2018)**.** *Food Habit* included vegetarian/non-vegetarian type, amount of diet taken per day along with smoking/alcohol/drug status**.** *Environmental Impact Study* contained CO_2 exposure, drinking water parameters (both physical and chemical) and sound pollution status**.** *Gynecological History* mainly included information about menstrual status of women**.** *Obstetrical History* contained information about mother and

child, previous pregnancy and delivery types with arisen complications. *Past Medical and Family History* parameters were also recorded in this section.

Stress Estimation was performed based upon 25 yes/no questions as suggested by Canadian Mental Health Association. After receiving the answers from the respondent, inputs were provided in the website (Canadian Mental Health Association, 2012) to get **Stress Index** of the preeclamtic patient. *Physiological and Clinical Profile* comprised of B.P. record, edema observed and bio-clinical investigations (Albumin, Serum Creatinine, R.B.C. and Platelet Count, etc.). *Confirmation and Follow up* section informed the basis upon which the patient was confirmed as preeclamptic. Subsequent advice and follow up were also included in this part. Finally *Outcome* section provided information on patient's delivery mode, mother and child's health status, placental information, etc.

4.6 Sample Size Determination

The sample size (n) was determined for 10,000 population based model (Equation 1). The estimated sample size would be about 87. In the study, 90 Preeclamptic patients were monitored. The sample size was determined as follows:

$$n = \frac{Z^2 pq}{d^2} \qquad (1)$$

where, **Z** is the area under normal curve corresponding to the desired confidence level (CI) and represents the amount of uncertainty that one can tolerate. In the study, Z = 1.96 for 95% CI.

p is response distribution or expected frequency distribution**.** In the study, p = 0**.**06 (Prevalence of preeclampsia was assumed to 6%)**.**

q = 1 – p = 0**.**94**.**

d = Tolerated margin of error**.** In this study, d was assumed as 5%, i.e., 0**.**05**.**

Therefore, $n\ (sample\ size) = \frac{(1.96)^2\ (0.06)(0.94)}{(0.05)^2} = 87$

In the study, Purposive sampling techniques were followed**.**

4.7 Ethical Consideration

The Ministry of Health and Family Welfare, the Government of the People's Republic of Bangladesh allowed the study to conduct**.** Moreover, permissions from the authority of concerned Upazilla Health Complex of Rajshahi district and Rajshahi Medical College Hospital, Rajshahi were taken for the study**.** The Ethical Certificate is attached in **Appendix 8.** The aim and objectives of the study along with its procedure, risks and benefits of the study were explained properly to the respondents in easily understandable language**.** When the participants were agreed to cooperate, their written consents were taken**.** It was assured that all the information and records would be kept confidential and the procedure would be used only for research purpose**.**

4.8 Patient Screening Techniques

In order to screen the pregnant women (especially 20 weeks gestation) for preeclampsia, firstly patient's B.P. was monitored twice (4 hours apart)**.** If B.P. was equal to or greater than 140/90 mm Hg, careful physical observations were made for edema and other relevant

complications (mentioned in Figure 18). Then the patient's bio-clinical investigation reports were analyzed for proteinuria (albumin in urine), serum creatinine, R.B.C. and platelet count. The elevated levels of proteinuria, serum creatinine and R.B.C. count, and lower level of platelet count confirmed preeclampsia (American College of Obstetricians and Gynecologists, 2013; Magee *et al.*, 2016).

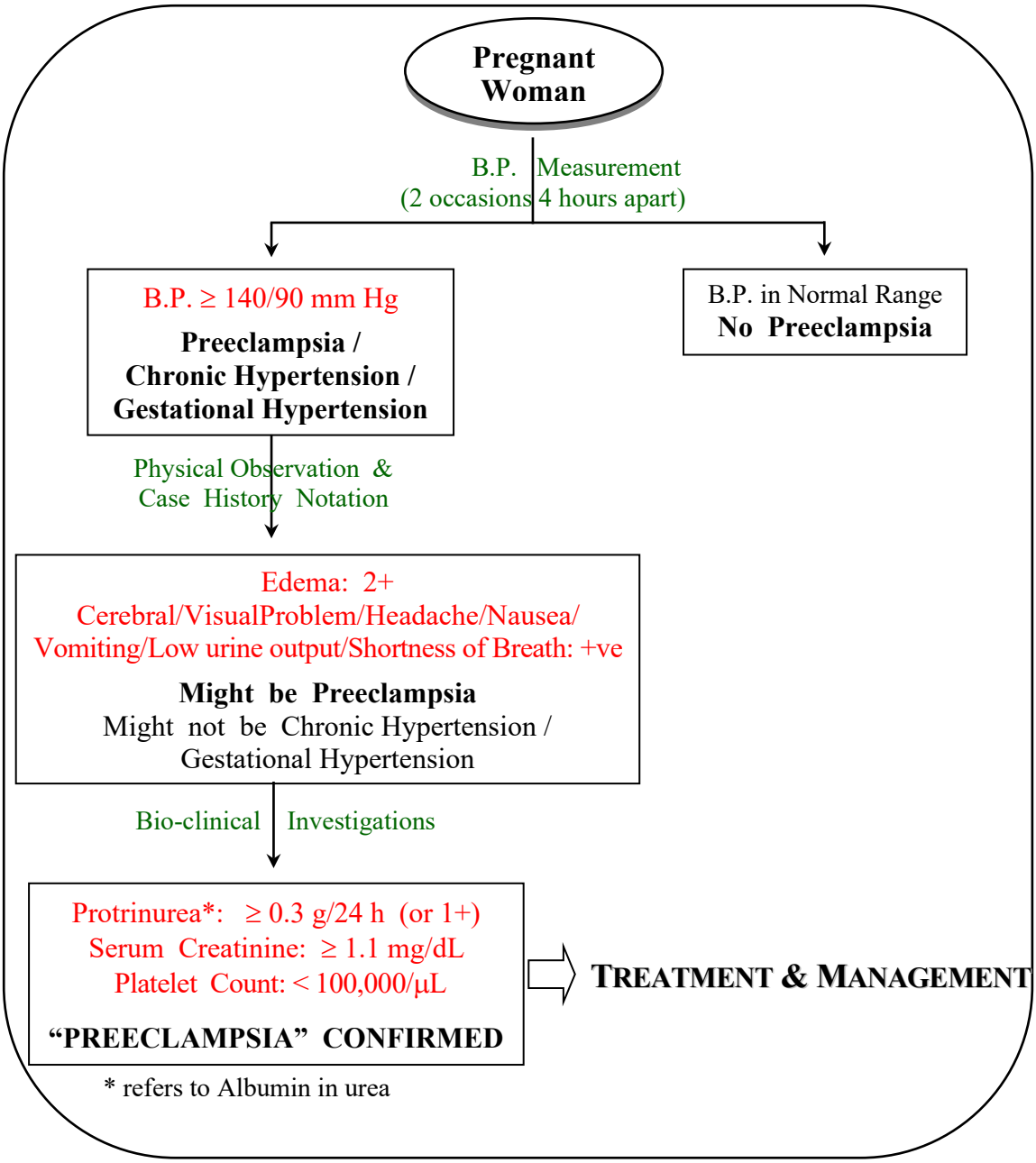


Figure 18. Flow-chart representing the screening of preeclampsia.

4.9 Study Type

The present investigation is mainly a 'Cross-sectional Study' with some Longitudinal Studies**.** Since it involves observational studies that analyze several types of data of the preeclamtic patients (a particular group) over specific time, describing relative risks from prevalence, it is a Cross-sectional Study**.** Since the investigation deals with several risk factor variables of the preeclamptic patients over time, it is also a longitudinal study**.**

4.10 Blood Pressure Measurement Technique

Blood pressure measurement in pregnancy should follow the same standardized technique as outside pregnancy (Pickering, 2005; Daskalopoulou, 2012; Hypertension Canada, 2018) and the 'Best Practice Points' for recommendations specific to pregnant women**.** In brief, the following steps were taken**:**

1. The woman must be **positioned** appropriately**:** seated, still, and with her legs uncrossed, feet flat on the floor, and her back resting on the back of the chair**.** Women should be in the sitting position that gives a blood pressure reading that reflects the true value; supine positioning has the potential to cause hypotension, and left lateral positioning has the potential to give a spuriously low reading, because the right arm is frequently elevated above the level of the heart during blood pressure measurement (Wichman *et al.*, 1984)**.**

2. The woman **should not talk, read, look at her phone/computer, or watch television.**

3. The woman's **arm should be resting at the level of her heart.** This may require use of a pillow**.**

4. The woman should **rest for 5 minutes** before her blood pressure is taken**.**

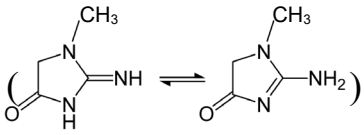
5. The **blood pressure cuff should be placed on the woman's bare upper arm**, and not over clothing**.**

6. The **blood pressure cuff must be the right size.** It must be long enough and wide enough**.** The length should cover two-thirds of the distance between her shoulder and elbow; the bottom should end up about 1–2 cm above the elbow**.** The width must be such that the inflatable part of the blood pressure cuff should go around about 80% of the woman's upper arm where the blood pressure is being measured**.** We kept in mind that if the cuff was too small (e.g., a 22–32 cm cuff used on a 35 cm circumference arm), it would overestimate sBP by 7–13 mm Hg and dBP by 5–10 mm Hg (Magee *et al.*, 2016)**.**

7. The blood pressure was measured using **appropriate technique for the machine in use.** ***Auscultatory Techniques*** that required a stethoscope and special training was utilized**.** Blood pressure was taken at least three times, with the first measurement discarded as it was the range-finding measurement**.** The second and third measurements were taken one minute apart and the average was the measurement for that visit**.** Korotkoff phase V (marked by the disappearance of Korotkoff sounds) was used for designation of dBP; compared to phase IV (marked by muffling of Korotkoff sounds)**.** Identification of phase V was more reliable (Shennan *et al.*, 1996) than that of phase IV and pregnancy outcomes were similar when either was used**.** Korotkoff phase IV was used for dBP only if Korotkoff sounds were audible as the dBP level approach 0 mmHg**.**

4.11 Bio-clinical Investigations

The principal bio-clinical investigations of preeclamptic patients included urinary albumin, serum creatinine, R.B.C. and platelet counts**.** Their detailed procedures are mentioned below**:**

A) Serum Creatinine: Creatinine () is a waste product of degradation of creatine, component of muscle**.** A serum creatinine test is a measure of renal health, i.e., reveals filtration performance of kidneys (Mayo Clinic, 2018)**.**

In serum creatinine test, the creatinine in extracted serum or heparinized plasma (Kaplan and Pesce, 2010) was allowed to react with alkaline picrate to form a red colored complex**.** The absorbance of the solution was measured at 492 nm with a DR/4000 U (HACH Company, Colorado, USA) UV-VIS Spectrophotometer after 30 (A_1) and 90 seconds (A_2) (SPINREACT, 2017)**.** Finally, the concentration was attained from the Absorbance ($A = A_2 - A_1$) from calibration curve**.**

B) Urinary Albumin: It is often called 'Microalbuminuria' that occurs when kidney leaks small amount of albumin into the urine**.** The quantitative estimation of urinary albumin was performed by

"Esbach's Albuminometer" (Khaleque and Mamun, 2011). The urine sample was first made slightly acidic with 5% (v/v) acetic acid. The urine was placed upto the mark 'U' and the reagent upto the mark 'R' of the Albuminometer. After inverting it several times to mix, it was allowed to stand vertically for 24 hours. The graduation at the top of the precipitate was recorded that provided the value of albumin in g/L of urine.

C) Platelet and R.B.C Count: The platelet and red blood cell (R.B.C.) in venous blood were counted using conventional methods (Khaleque and Mamun, 2011; SPINREACT, 2017). For this Bright-Line™ Haemocytometer of model Z 359629 (Sigma-Aldrich, USA) was employed. First venous blood was collected into K_3-EDTA. The blood was drawn upto mark 1 followed by withdrawing platelet diluting fluid upto mark 101 in a dry RBC pipette (Alex Edutech Exporter, India). Mixing diluted the blood 100 times. After filling the counting chamber it was allowed to stand for 2-3 minutes for R.B.C. and 30 minutes for platelets. The chamber was then placed under a microscope, adjusted the amplification power and counted R.B.C. and platelets according to the lines.

4.12 Data Collection

Based upon the sources, the data incorporated in the study can be classified as primary and secondary**.** The primary data were collected by interviewing the patients (**Appendix 8**), physical examinations (**Appendix 9**) and by analyzing patient's Pathological Profile (containing the reports of urine, blood, etc.)**.**

BMI, Socio-economic Index and Stress Index were estimation *Online* (Canadian Mental Health Association, 2012; NIH, 2018; The New York Times, 2018) with the help of gathered primary data**.** The physical and chemical properties of aquifer groundwater that the patients' take as drinking water were adapted from British Geological Survey's datasets (n=3,540) in Bangladesh (BGS, 2001)**.** These data were considered as secondary**.**

4.13 Quality Control

Prior to utilization of any apparatus/instrument, it was calibrated properly**.** Such calibration was also made for even sphygmomanometers (please refer to Result and Discussion section)**.** For recoding patient's B.P., average value of both mercury and aneroid sphygmomanometers' readings were considered**.** Sometimes, it was cross-checked with the reading taken by a highly skilled surgeon**.** Sometimes during interview, the right answer was collected by side

question or discussion. Patient's pathological reports were only accepted when those were examined by certified and highly skilled pathologists. The preeclamptic patients were monitored regularly. The bio-clinical investigation reports were only accepted when those were performed with at least 5 point calibration with *r* (Pearson correlation coefficient) value of 0.998 or better.

4.14 Statistical Analyses

The datasets obtained were treated separately for analyzing basic statistical parameters and for making cross-tabulations and cross-plots. The SPSS (release 20.0), STATGRAPHICS Centurion (release 18.1.01) and Microsoft Excel (release 12.0) were employed for the purpose. Mathematical models were established based on simple and multiple regression analyses. The models were cross-checked by analyzing ANOVA, *P* value, *r* value (Pearson correlation coefficient), Durbin–Watson statistics and 'Lack-of-Fit' test. For these, Curve Expert (release 1.40) and STATGRAPHICS Centurion software were employed. The Box-Whisker plot was constructed using SPSS.

CHAPTER FIVE :

RESULTS AND DISCUSSIONS

5.0 Results And Discussions

The results or outcomes obtained from this investigation are illustrated in the following sections with proper discussions**:**

5.1 Comparison of Mercury and Aneroid Sphygmomanometers

In the study for patients' blood pressure (B.P.) measurements, two high precision sphygmomanometers were employed - *Nova-presameter® mercury sphygmomanometer* (Riester, Jungingen, Germany) and FDA approved SP-110 *Santadical® Aneroid Sphygmomanometer* (SantaMedcal, Los Angeles, USA)**.** The 3M™ Littmann® Master Classic II Stethoscope (New York, USA) was employed to complete B.P. monitoring**.**

A comparison (n = 82) was made to understand the actual performance of both the sphygmomanometers (Figure 19)**.** For this the same standardized technique (Pickering, 2005; Daskalopoulou, 2012; Hypertension Canada, 2018) was followed and the 'Best Practice Points' recommended for pregnant women (Magee *et al.*, 2016)**.** For the comparison the other variables were kept constants and the same patient was chosen for each B.P. measurement**.**

Least-square regression analysis yielded y = 1**.**075x - 5**.**224 (R^2 = 0**.**987)**.** The dashed line indicates a 1**:**1 correlation**.** Aneroid measurements yielded slight greater values than those of mercury measurements, especially at higher diastolic blood pressures ($P < 0.001$ by paired t-analysis at 99% CI)**.**

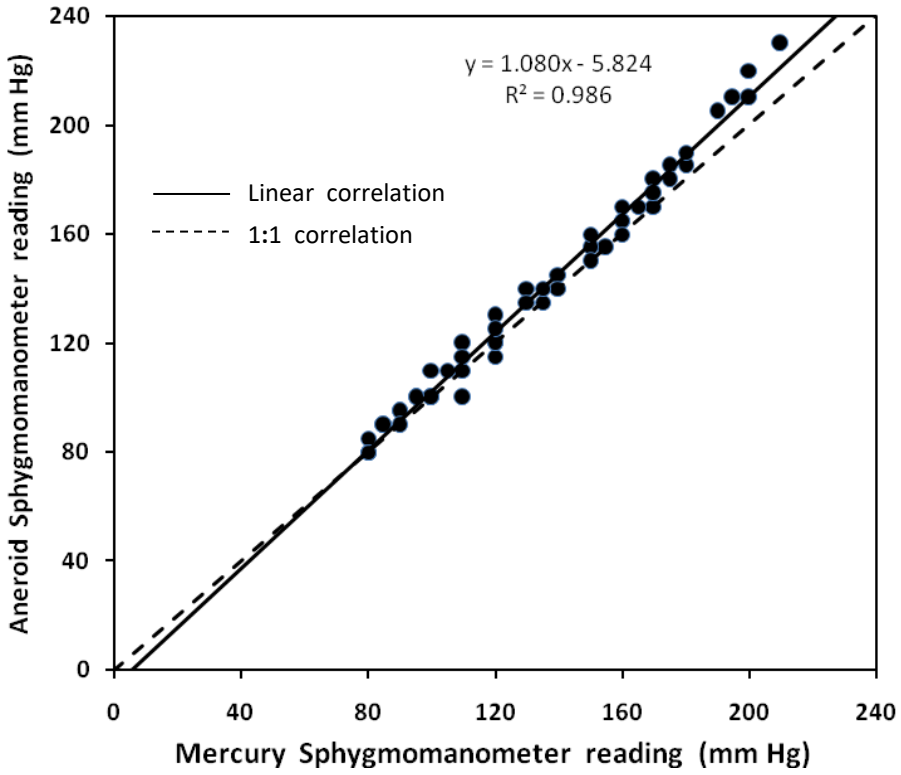


Figure 19. Correlation of B.P. measurements with mercury and aneroid sphygmomanometers**.**

Since the overall correlation between mercury and aneroid sphygmomanometers were roughly 1**:**1, aneroid instrument was utilized for B.P. measurements for most of the hypertensive patients**.** Because the aneroid instrument is easy to carry, smaller in size and free from contamination of mercury vapor (Turner *et al.*, 2007)**.**

The sphygmomanometers utilized in the present investigation to monitor blood pressure of preeclamptic patients were also employed by other authors (Rath and Fischer, 2009; Zibaeenezhad *et al.*, 2010) for estimation of pregnancy induced hypertension**.** They reported the instruments as of Gold Standard**.**

5.2 Prevalence of Preeclampsia

Rajshahi Medical College Hospital (RMCH) is a tertiary referral hospital that keeps the records of the patients properly. We collected 5 year-data (from 2013 to 2017) from RMCH that were sent to Ministry of Health and Family Welfare of Government of the Peoples Republic of Bangladesh. Based on the data, we found that the number of pregnant mother admitted into RMCH for delivery or obstructed complications increased from 11,532 to 17,201 (Figure 20).

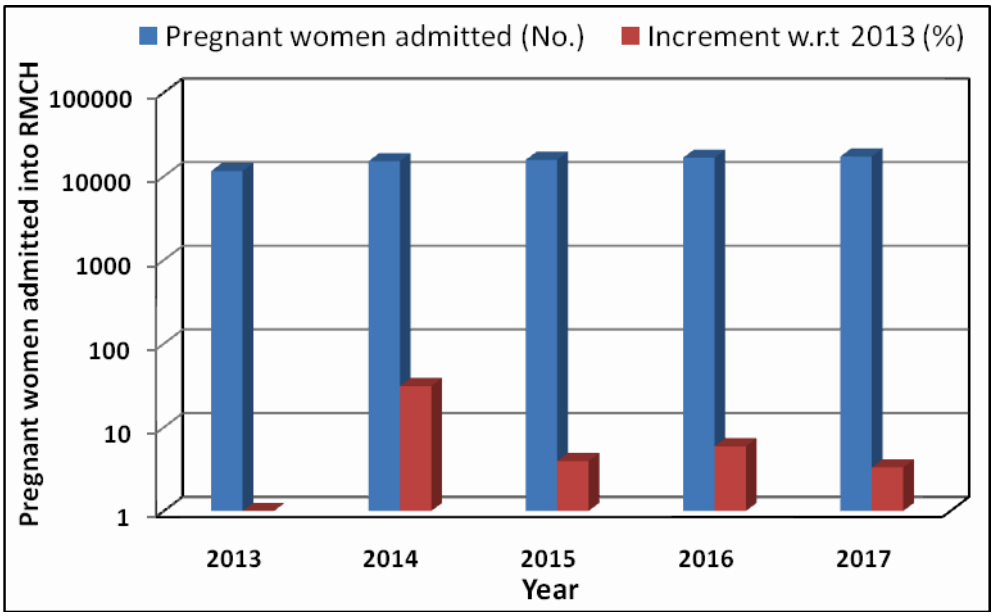


Figure 20. Pregnant mother admitted into RMCH for delivery or obstructed complications (on logarithm scale).

Among the RMCH admitted pregnant mothers for delivery or with obstructed complications, the distribution of preeclampsia is represented in Table 11. It is to be noted that besides RMCH, the other hospitals/clinics did not maintained the records of preeclampsia properly and hence here not considered.

Table 11. Distribution of preeclamptic patients in RMCH from 2013 to 2017.

Distribution	Year					
	2017	**2016**	**2015**	**2014**	**2013**	**Average**
Total No. of pregnant mother admitted into RMCH	17,201	16,648	15,716	15,119	11,532	15,243
No. of preeclamptic patients	435	538	493	547	407	484
% of preeclamptic patients	2.53	3.23	3.14	3.62	3.53	3.21

Table 11 reveals that the average number of preeclamptic patients found in RMCH per year is 484 (during the last five years). This is equivalent to 3.21% of total pregnant mothers admitted into RMCH for delivery or with obstructed complications. This finding is very close to WHO's (2003) report on incidence rate of preeclampsia (2.80%) (Table 6). The preeclampsia incidence rates in many Asian countries like India, Pakistan, Nepal, Myanmar, Korea, Bhutan, Iran, Thailand, Indonesia and Malaysia were reported (WHO, 2003) as 2.8%. The same rates were also found in many African countries like Egypt, Ghana, Algeria, Ethiopia, South Africa, Tanzania, Kenya, etc. But in some developed countries like Canada, USA, Australia, Belgium, Denmark, Germany, UK, France, Spain, etc., the preeclampsia incidence rates were as low as 0.4% (WHO, 2003). Our observed preeclampsia incidence rate was slightly higher than the values for the Asian countries.

In order to understand the trend of preeclampsia incidence rate with respect to time, Figure 21 is plotted. Obviously, the rate of preeclampsia in pregnant women in Rajshahi region is decreasing. This is probably due to increase in consciousness of the pregnant women and their attendants. The initiatives taken by the Government of Bangladesh for free educational policies for females and increase in per capita income undoubtedly play a significant role behind this.

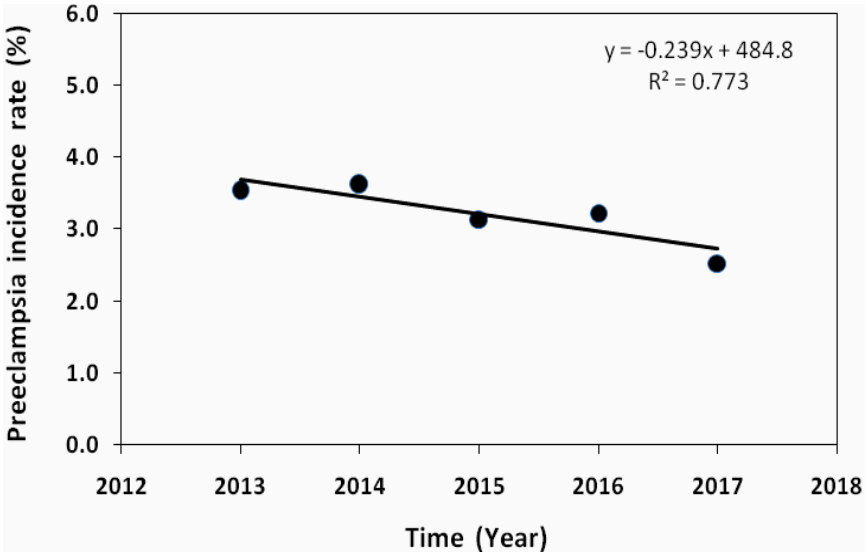


Figure 21. Trend of preeclampsia incidence rate in RMCH with respect to time.

Extrapolation of the trend line in Figure 18, with the aid of the software Curve Expert (version 1.4), reveals that in the years 2020, 2023 and 2026 the preeclampsia incidence rate should be 2.02%, 1.30% and 0.58% respectively. In 2027, our preeclampsia incidence rate should be equal to that (0.4%) of the developed countries, provided that the trend is followed exactly.

5.3 Distribution of Preeclamptic Patients based on Age

In this study, the age of the participating preeclamptic patients ranged from 16 to 40 years, with an average of 25.90 ± 0.65 years. The age wise distribution of preeclamptic patients is represented in Table 12. It is obvious from the Table that 69% of the preeclamptic patients were below the age of 29 years. About one-fourth of the preeclamptic mothers were below 20 years, whereas only 1% mother was at 40 years. This reflects that the youngest mother are at high risk of preeclampsia.

Table 12. Age wise distribution of preeclamptic patients.

Age of mother (Year)	Distribution of Preeclamptic Patients	
	Number	Percentage
≤ 20	22	24.45
21 – 24	20	22.22
25 – 29	20	22.22
30 – 34	15	16.67
35 – 39	12	13.33
≥ 40	01	1.11
TOTAL	**90**	**100.00**

The ANOVA (Table 12a) shows that the differences in the incidence of preeclampsia among different age groups was found to be statistically significant ($p < 0.05$).

Table 12a. ANOVA showing the effect of age on the distribution of preeclamptic patients.

	Sum of Squares	df	Mean Square	F
Between Age Groups	756.286	15	50.419	1.437
Within Age Groups	2595.814	74	35.079	
Total	3352.100	89		

The age wise frequency distribution of preeclamptic patients is represented in Figure 22. In the Figure, the red curvature shows normal distribution curve.

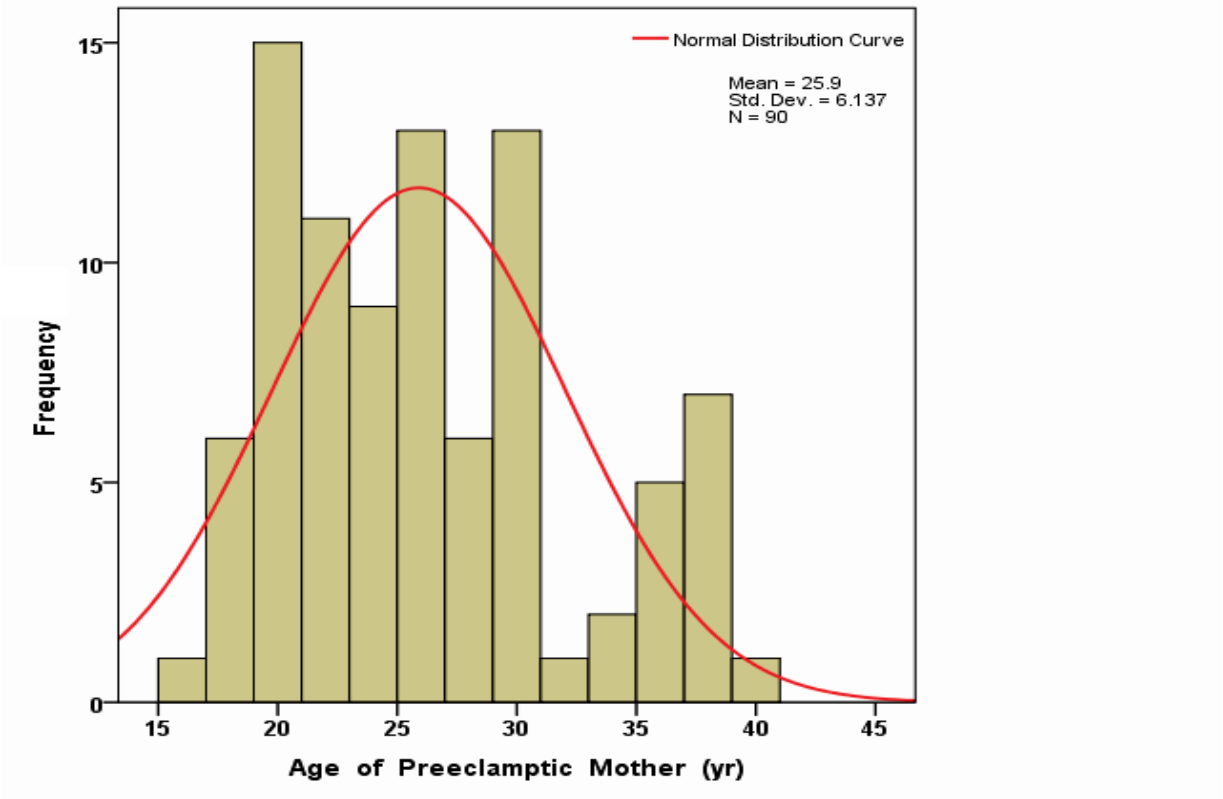


Figure 22. Agewise frequency distribution of preeclamptic patients.

Our findings are in accordance with many authors. Parra-Pingel *et al.* (2017) found that in Ecuador amongst severe preeclamptic patients, 13.5% were aged 19 or less years and had singleton pregnancies. Kawakita *et al.* (2016) found that the prevalence of preeclampsia might be twice as higher in adolescents. This might be due to physical immaturity and overlapping maternal growth, nutritional status, socio-economic factors, partner abuse and emotional overload. Bakwa-Kanyinga *et al.* (2017) also reported that in Brazil among 17.8% teenage mothers 5.3% presented preeclampsia. Puerperal complications and prematurity were more frequent to them.

5.4 Distribution of Preeclamptic Patients based on Health Type

Body mass index (BMI) is a measure of body fatness**.** The BMI of preeclamptic patients were estimated based on the equation: BMI = Body weight (kg) / Body height $(m)^2$**.** Based upon the BMI values obtained, the preeclamptic patients were classified as Underweight (< 18**.**5), Normal (18**.**5 – 24**.**9), Overweight (25 – 29**.**9) and Obese (≥ 30)**.**

The prevalence of preeclamptic patients based on health type within the study period is represented in Figure 23**.** It was observed that as the patients were more obese, the occurrence of preeclampsia was increased more**.** Out of the 90 preeclamptic patients, 36 (40%) were obese, 26 (29%) were overweight, 26 (29%) were also normal and only 2 (2%) underweight**.**

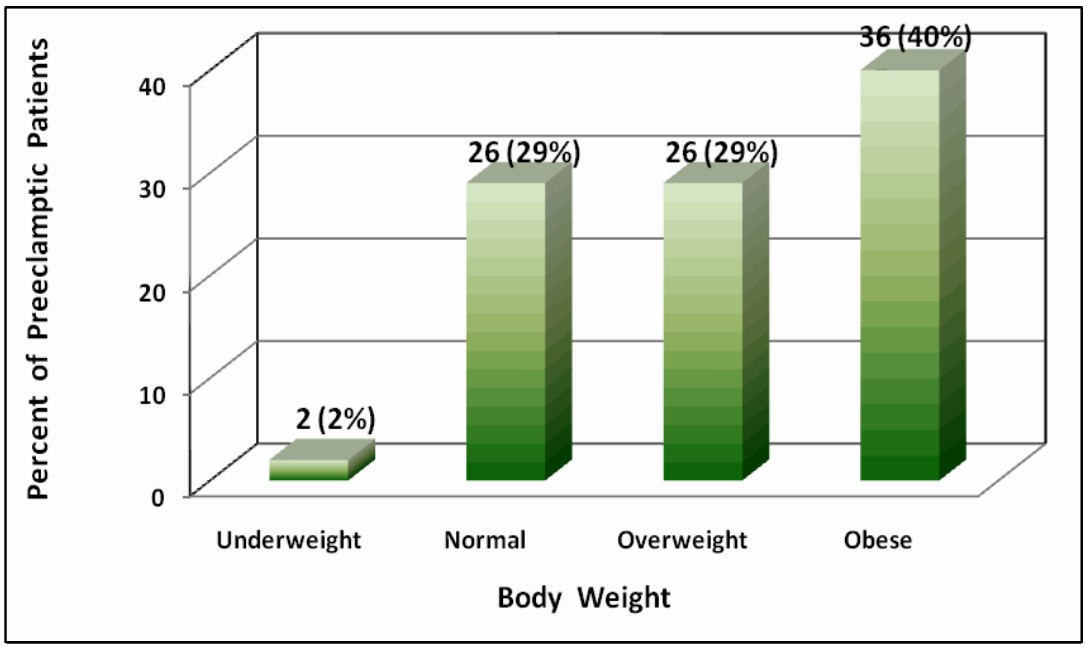


Figure 23. The effect of body weight on the distribution of preeclamptic patients**.**

It was estimated the weight gain of the preeclamptic mothers (n = 32) at 40 weeks gestation from online pregnancy weight gain calculator (Maple Tech, 2018). On an average, the gained weight for the pregnant women was 11.3 - 15.9 for normal, 6.8 - 11.3 for overweight and 5.0 - 9.1 for obese mother.

It was also found that obese or overweight pregnant preeclamptic mothers were associated with some additional complications. These included severe edema, severe headache, vomiting, lower abdominal pain and hyperacidity.

A recent meta-analysis concluded that overweight/obesity as well as maternal adiposity is associated with an increased risk of preeclampsia (Wang *et al.*, 2013). Increased BMI is an important risk factor for preeclampsia and severe preeclampsia with an attributable risk of 64% (Pare *et al.*, 2014). This risk (Bodnar *et al.*, 2005) may be increased two- to three-fold as BMI increases from 21 kg/m^2 to 30 kg/m^2. In the present study, obese preeclamptic patients were found as vulnerable.

5.5 Distribution of Preeclamptic Patients based on Blood Groups

It was observed that the studied preeclamptic patients' had mainly A+, B+ or O+ blood groups (Figure 22). The percentage rate of preeclampsia based on patients' blood grouping was as follows: A+ (39%) > B+ (33%) > O+ (24%) > AB+ (2%) = O– (2%). It is interesting to note

that no preeclamptic patients had A–, B– and AB– blood groups and only 2% patients had very rare O– blood group. The comparison of blood groups between Bangladeshi national population (Wikipedia, 2018a) and the present population are presented in Figure 24.

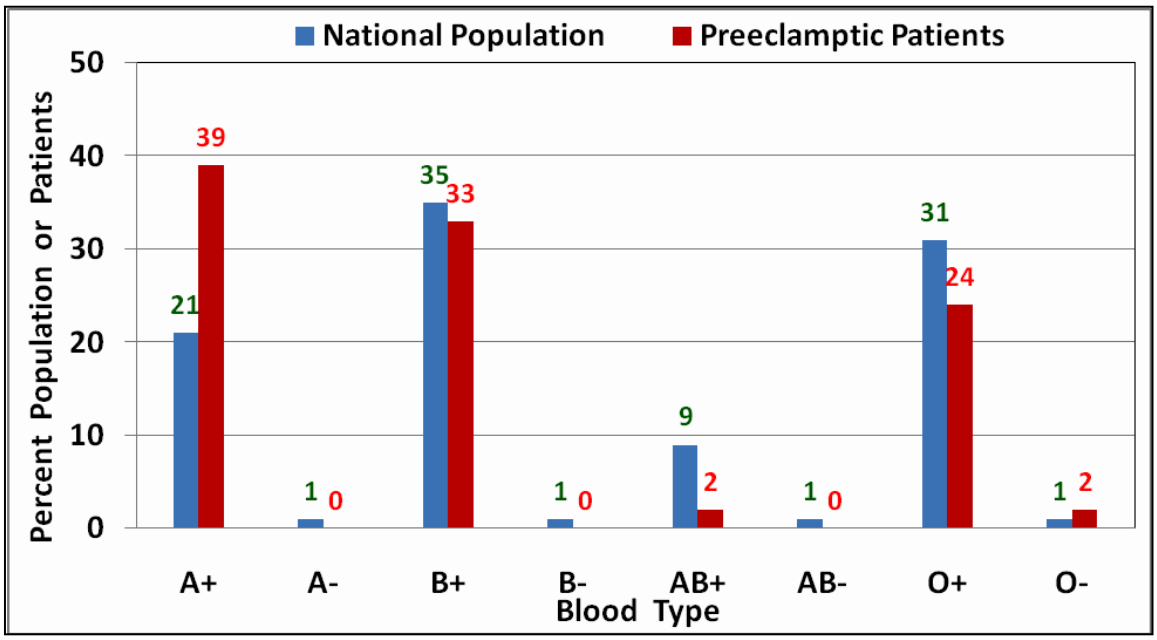


Figure 24. Blood groups of the studied preeclamptic patients.

In Turkey, it was found (Avci *et al.*, 2016) that the risk of developing preeclampsia was significantly higher in group AB than other blood groups (P=0.006). The risk of developing hypertension after preeclampsia was significantly higher in group O than other blood groups (P=0.004). This was attributed to an abnormal hemostasis occured in the uteroplacental circulation of women with preeclampsia, the association between AB blood group and preeclampsia might reflect the multifactorial character of thrombus formation (Higgins *et al.*, 1998). AB blood group subjects present

increased levels of two important hemostatic factors, factor VIII and von Willebrand factor (VWF), and increased levels of these two hemostatic factors had been related to increased risk for thrombus formation in several conditions (Bowen, 2003). The molecular mechanism of the effects of ABO on VWF was not completely understood. The most accepted hypothesis was that: ABO antigens would influence VWF glycosylation and therefore its plasma levels by preventing its proteolysis and clearance by ADAMTS13, a metalloprotease able to cleave VWF multimers. Posttranslational modification of VWF included addition of sugar residues, the same that defined ABO antigens. These sugar residues were located near the ADAMTS13 cleavage site on VWF molecule and might influence its proteolysis by steric hindrance or charge effects (Bowen, 2003).

5.6 Distribution of Preeclamptic Patients based on Educational Levels

In the study it was found that out of the 90 preeclamptic patients, 25 (27.78%) had completed secondary level education, which was equivalent to S.S.C. (Secondary School Certificate) in Bangladesh. Following this, 18 (20.00%) of the patients acquired junior level education (equivalent to J.S.C.) and 17 (18.89%) primary level education (equivalent to P.E.C.). Out of 90 respondents, 8 (8.89%) preeclamptic patients had the higher secondary education level. On the contrary, 14 (15.56%) preeclamptic patients were graduates. The Masters level education completion patients were only 4 (4.44%). The 4 (4.44%) preeclamptic patients were also illiterate.

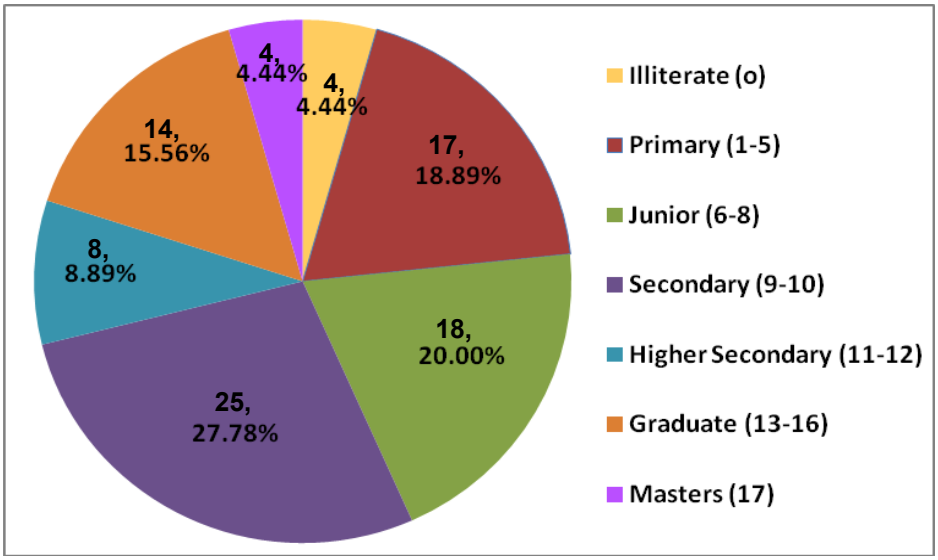


Figure 25. Distribution of the preeclamptic patients based on educational level.

Figure 25 reflects that vulnerable preeclamptic patients were under matriculated, which was 66.67%. Thus two-thirds of the patients completed education level 10. This means that the preeclamptic patients were not very conscious about preventing preeclampsia. The individual education level wise distribution of the patients are represented in Figure 26.

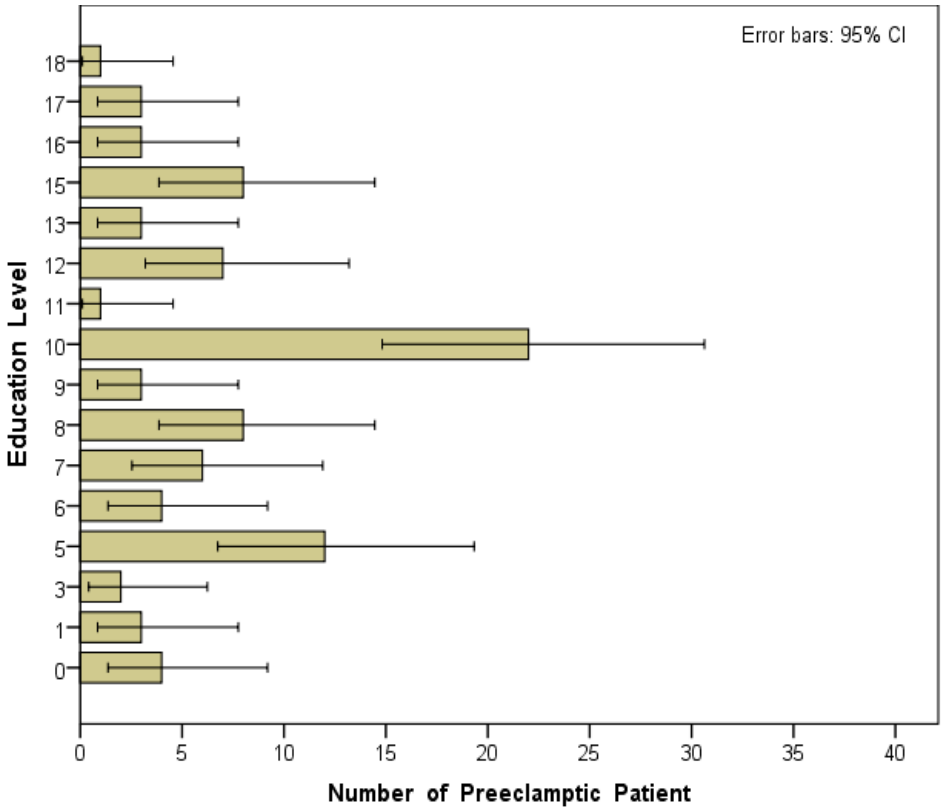


Figure 26. Individual education levelwise distribution of preeclamptic patients.

Bayat *et al.* (2016) reported that in Iran, the preeclamptic mother's education level was as follows: Illiterate (0%), below high school education (42.3%), high school diploma (20.5%) and university degree (37.2%). Thus the Iranian women's education level was higher than the Bangladeshi women. Saxena *et al.* (2014) found that in Uttar Pradesh (UP) of India, the education level of preeclamptic patients were poor, below Bangladeshi level. They reported illiterate, up to 8^{th} standard, 9^{th} to 10^{th}, 11^{th} to 12^{th}, graduation and post-graduation patients as 40.00%, 32.86%, 5.71%, 11.43%, 7.14% and 2.86% respectively. In the present study the educational levels of the preeclamptic patients are representative of Southern Asia. And it was obvious that low educational attainment were significantly associated with higher risk of preeclampsia.

5.7 Distribution of Preeclamptic Patients based on Socio-economic Indices

Socio-economic Index (SEI) is a measure of social class, which was determined from patient's occupation, education, income level and wealth. It was found that out of 90 preeclamptic patients, 69 were within the SEI range of 10 – 30, whereas 21 were above the range. This means that about three-fourths of the concerned patients

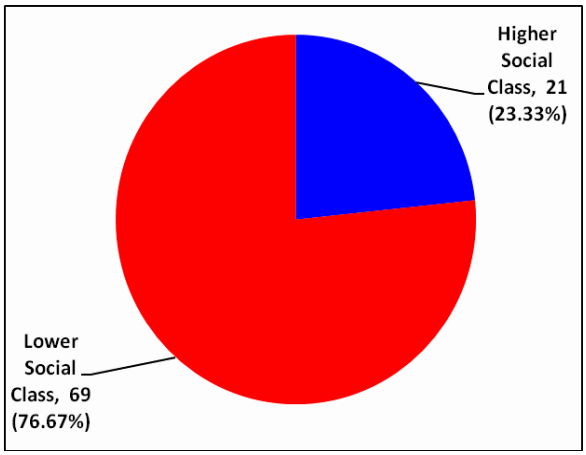


Figure 27. Distribution of Socio-economic Indices of preeclamptic patients.

were of lower social class (Figure 27). The reasons included that the vulnerable patients were housewife having low income and wealth and were not properly educated. The socio-economic indices of individual patients are presented in Figure 28.

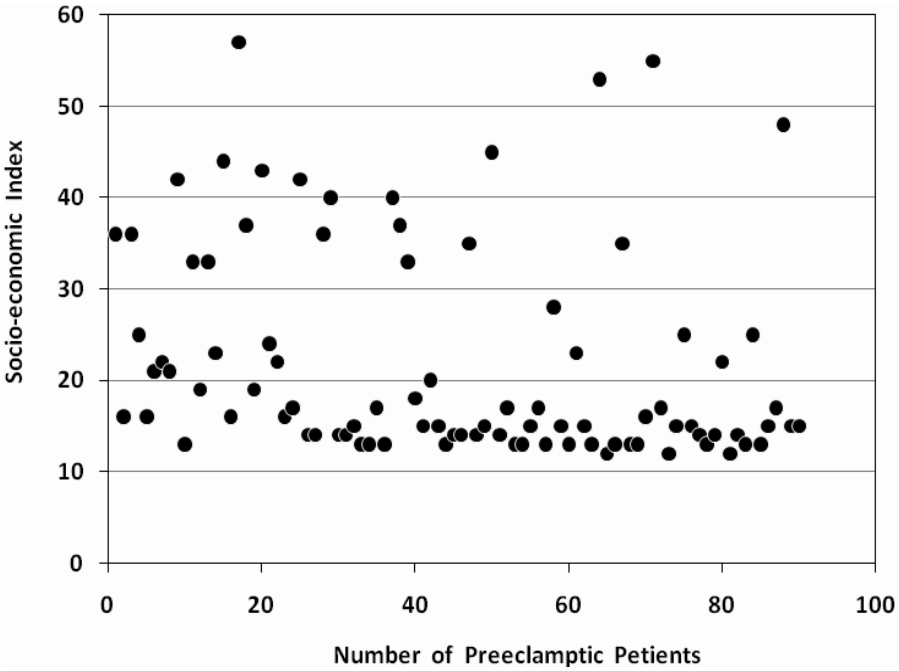


Figure 28. Socio-economic Indices of individual patients.

5.8 Some Demographic Information of Preeclamptic Patients

The central tendency indicating the location of the distribution were measured by mean and median; dispersion showing the dissimilarity of the values by range, standard deviation and variance; the shape of the distribution by skewness and confidence interval (95% level) for the mean; and the tailedness (extreme values in either tail) of distribution by kurtosis. These were analyzed for each demographic dataset of preeclamptic patients using SPSS. The analysis results are represented in Table 13.

Table 13. Statistical analyses on some demographic data of the preeclamptic patients.

Variable	Unit	n	Range	Median	Mean ± SE	95% C.I.[a] for mean	Standard Deviation	Variance	Skewness	Kurtosis
Age	yr	90	16 – 40	25.00	26.34 ± 0.73	24.88 – 27.80	5.888	34.665	0.455	-0.575
Body weight	kg	90	45 – 82	62.00	26.34 ± 0.73	61.07 – 65.53	9.018	81.319	0.237	-0.369
Height	cm	90	127 – 167	152.00	26.34 ± 0.73	150.78 – 154.21	6.915	47.816	-1.546	3.336
BMI	$kg\,m^{-2}$	90	17 – 38	27.30	26.34 ± 0.73	26.16 – 28.45	4.610	21.248	0.290	-0.433
Education	–	90	0 – 18	10.00	26.34 ± 0.73	8.31 – 10.49	4.401	19.369	-0.182	-0.451
Monthly income	Tk	90	0 – 20,000	0.00	26.34 ± 0.73	492 – 2,185	3,418	1.168×10^{7}	4.158	18.682
Wealth	Tk	90	0 – 3,000,000	100,000	26.34 ± 0.73	149,930 – 407,916	520,580	2.710×10^{11}	3.713	15.700
Socio-economic Index	–	90	12 – 57	15.00	26.34 ± 0.73	19.30 – 24.98	11.467	131.496	1.283	0.575

[a] C.I. stands for Confidence Interval.

The percentile distribution on the basis of weighted average and Tukey's Hinges of each of the demographic parameters are given in Table 14.

Table 14. Percentile distribution some parameters of demographic information of preeclamptic patients.

		Percentiles						
		5	10	25	50	75	90	95
Weighted Average (Definition 1)	Age	18.00	19.00	22.00	25.00	30.00	36.00	37.00
	Body_Weight	48.00	53.00	58.00	62.00	69.50	75.40	80.70
	Body_Height	135.60	143.00	152.00	152.00	157.00	158.20	161.40
	BMI	20.80	21.56	23.65	27.30	30.50	34.60	34.98
	Education	1.00	4.20	6.00	10.00	12.00	15.40	16.70
	Monthly_Income	.00	.00	.00	.00	1500.00	3400.00	8500.00
	Wealth	.00	.00	45000.00	100000.00	275000.00	1000000.00	1000000.00
	SEI	13.00	13.00	14.00	16.00	33.00	40.80	43.70
Tukey's Hinges	Age			22.00	25.00	30.00		
	Body_Weight			58.00	62.00	69.00		
	Body_Height			152.00	152.00	157.00		
	BMI			23.80	27.30	30.30		
	Education			6.00	10.00	12.00		
	Monthly_Income			.00	.00	1000.00		
	Wealth			50000.00	100000.00	250000.00		
	SEI			14.00	16.00	33.00		

5.9 Distribution of Preeclamptic Patients based on Some Demographic Characteristics

A) Religion: Out of the 90 preeclamptic patients, 80 (88.89%) were Muslims and 10 (11.11%) Hindus, no Christians and Buddhists were found (Figure 29 A). This is in accordance to Bangladesh Population and Housing Census 2011 (BBS, 2014), that estimated Muslims, Hindus and Others (Christians, Buddhists, etc.) in Bangladesh as 90%, 9% and 1% respectively.

B) Family Structure: It was found that 38 patients (42.22%) were from Single Families, whereas 52 (57.78%) from Joint Families (Figure 29 B). Verma *et al.* (2017) found that in Jaipur of India, there was 1.22 times more risk of preeclampsia in joint families than in single families.

C) Color: Regarding ethnicity all were local women, not migrated. Among the pregnant women, 55 (i.e., 61.11% of total) were white, 12 (13.33%) were grey and 23 (25.56%) were black (Figure 29 C).

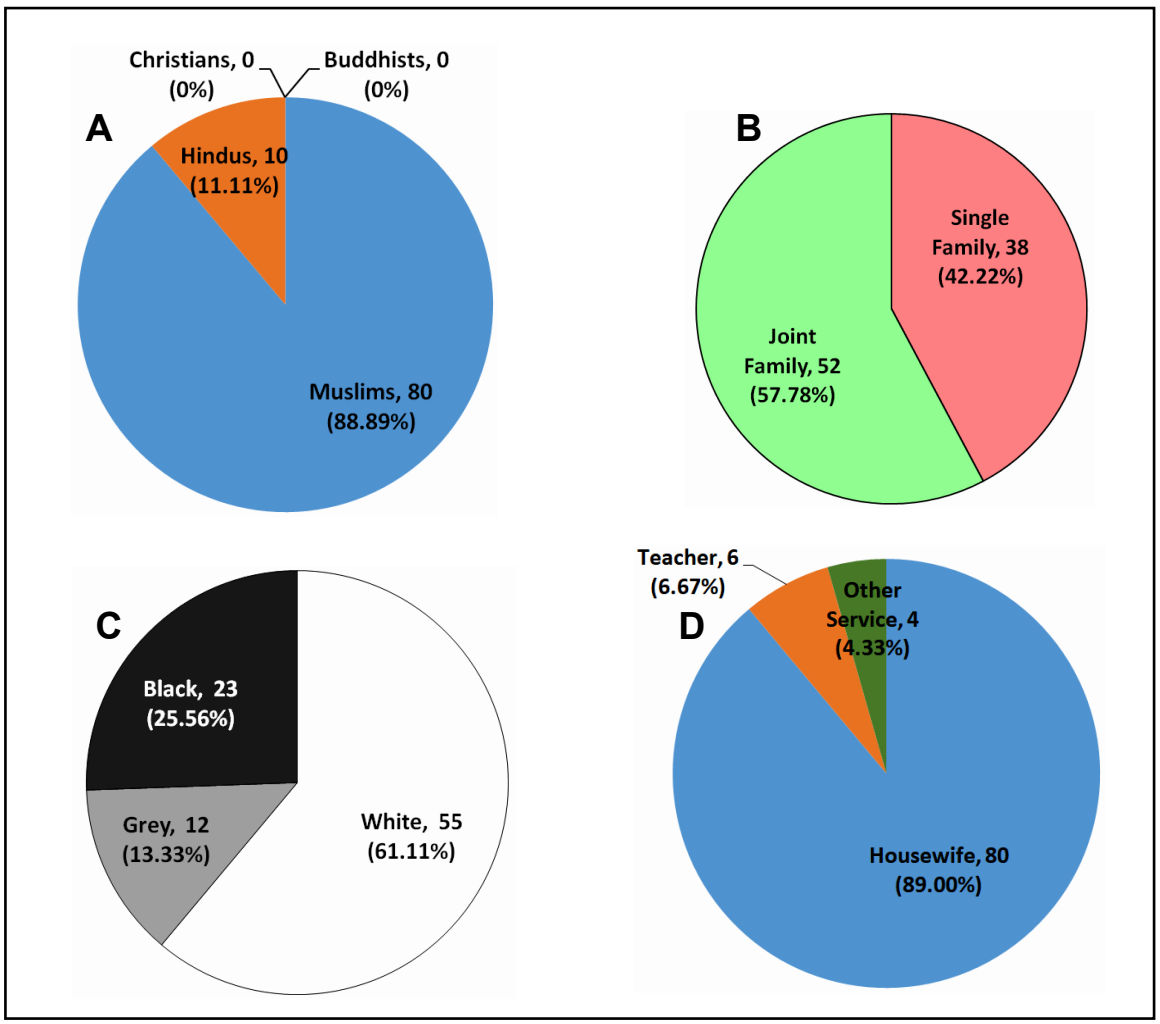


Figure 29. Distribution of Preeclamptic Patients. [**A:** Religion; **B:** Family Structure; **C:** Color; **D:** Patients' Occupation]

D) Patients' Occupation: On the basis of the preeclamptic patients' occupation, 80 (88.89%) were housewives, 6 (6.67%) were teachers and 4 (4.44%) were in other services (Figure 29 D). In other services, NGO (Non-Government) related jobs dominated.

5.10 Distribution of Preeclamptic Patients based on Food Habits

It was found that the pregnant women and their attendant were conscious about food habits and hence took more proteins, vegetables and fruits. Meat, fish, egg, pulse and milk were the main sources of proteins. According to Household Income and Expenditure Survey conducted by Bangladesh Bureau of Statistics in 2010, pulse, fish, meat, egg and milk intake rate by Bangladeshi people were 14.3, 49.5, 19.0, 7.2 and 33.7 gram per capita per day respectively (HIES, 2011). In the study the intake rate of the above values corresponded to Higher Protein Intake, whereas below Lower Protein Intake. The vegetables and fruits intake rates were 166.1 and 44.7 gram per capita per day respectively (HIES, 2011). The Pie-chart 30 reflects that the pregnant women took higher amounts of both proteins and vegetables. This reflects their conciseness and probably acted as one of the factors that inhibit conversion from preeclampsia to eclampsia (Magee *et al.*, 2016).

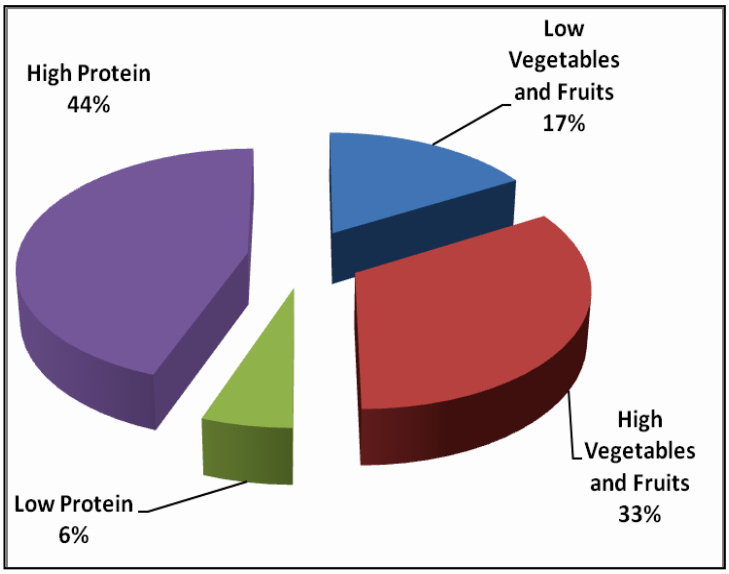


Figure 30. Protein and vegetables intake status of the pregnant women.

Young children, pregnant and lactating women have increased fluid requirements. Especially pregnant women require additional fluid replacement to ensure that foetal needs are met, as well as providing for expanding extra-cellular space and amniotic fluid. World Health Organization has set the requirement of drinking water for adult female as 2.2 L/day (WHO, 2004). It was found that on an average 15, 29 and 46 pregnant women (comprising 16.67, 32.22 and 51.11% of total women respectively) took drinking water above, at and below 2.2 L/day respectively. This means that roughly half of the women did not fulfill the requirement of drinking water. But most of the women took milk as 200 mL/day, although a few were unable to afford it or were unable to drink it. Please be noted that the amount was not exact, but estimated. According to the patients' statement, they neither smoke nor took alcohol or illicit drug during pregnancy.

5.11 Impact of Environmental Pollution on Preeclamptic Patients

It is well established that environmental pollutions impose adverse effect to human health, causing a lot of physiological and mental problems. This may induce severe hypertension that in turn might lead to preeclampsia. That's why, an attempt was taken to estimate the extent of environmental pollution exerted on preeclamptic patients. By environmental pollution, we mean Air Pollution, Sound Pollution and Groundwater Pollution. These are discussed below:

A) Air Pollution: Both the distance of living room from kitchen and room ventilation were treated a qualitative measure of CO_2 exposure. Most of the patients' living rooms were within 15 feet from kitchen. The peak of the Normal Distribution Curve in Figure 31 reflects this.

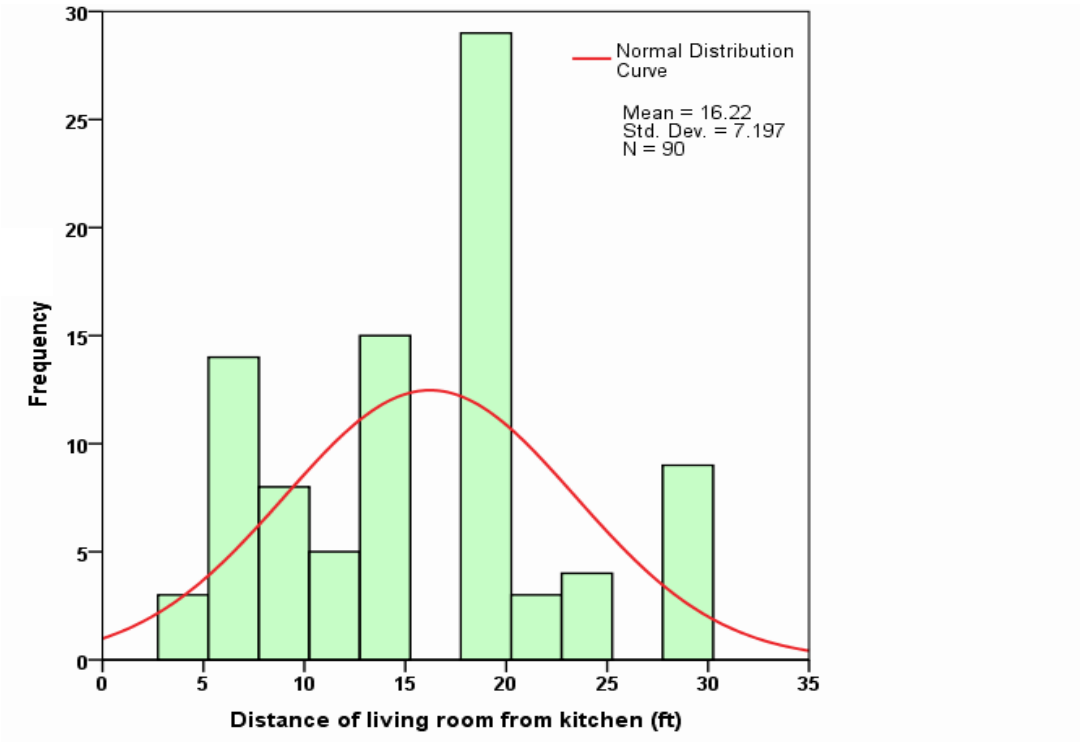


Figure 31. Frequency of distance of living room from kitchen.

The room ventilation status of the studied preeclamptic patients is depicted in Figure 32**.** It shows that 10% patients had good room ventilation; the remaining 90% patients had either moderate or poor bed room ventilation**.** Combination of distance of living room from kitchen and room ventilation reveals that the preeclamptic patients were subjected to moderate CO_2 exposure**.** Thus it might be a risk factor of preeclampsia**.**

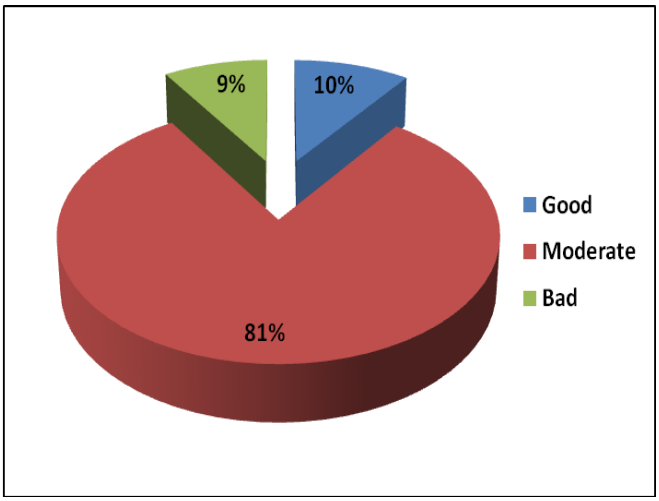


Figure 32. Room ventilation status of the preeclamptic patients **.**

B) Sound Pollution: Both the road distance from the living room and traffic condition of the road were considered as a qualitative measure of sound exposure**.** Based upon the patients' statement, the distances of the preeclamptic patients' living rooms from nearest road were estimated and cross-checked with their attendants' statement**.** The findings are represented in Figure 33**.**

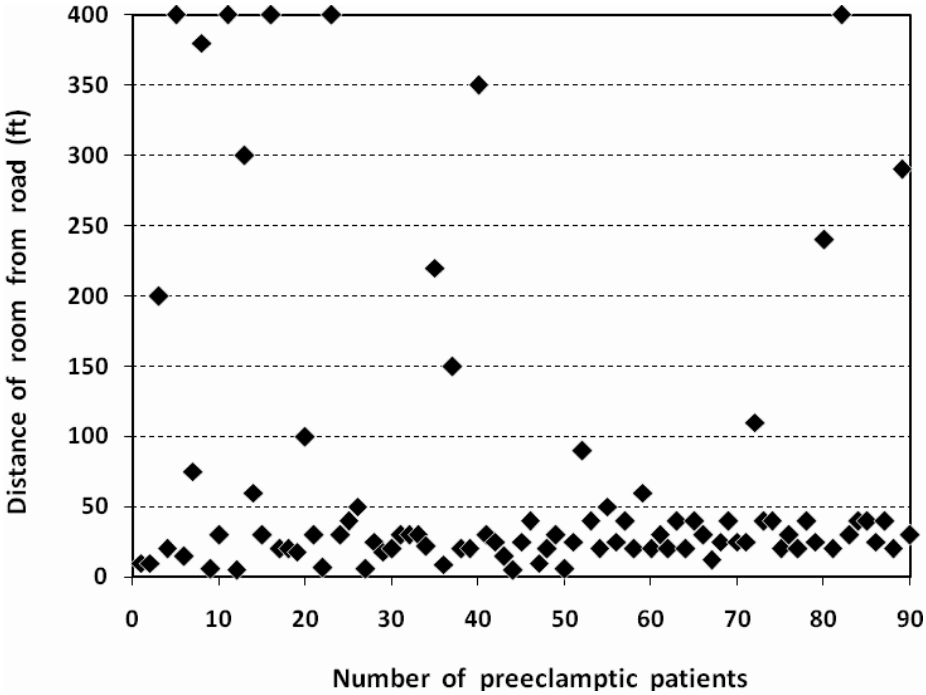


Figure 33. Distance of living room from nearest road of preeclamptic patient.

It was found that 78.89% of the preeclamptic patients' living rooms were below 50 ft from the nearest roads. The value was 84.44% for 100 ft distance. Therefore, it is reasonable that they would experience sound pollution. In order to understand it, the traffic conditions and other potential sources of sound pollutions were noted and represented in Figure 34.

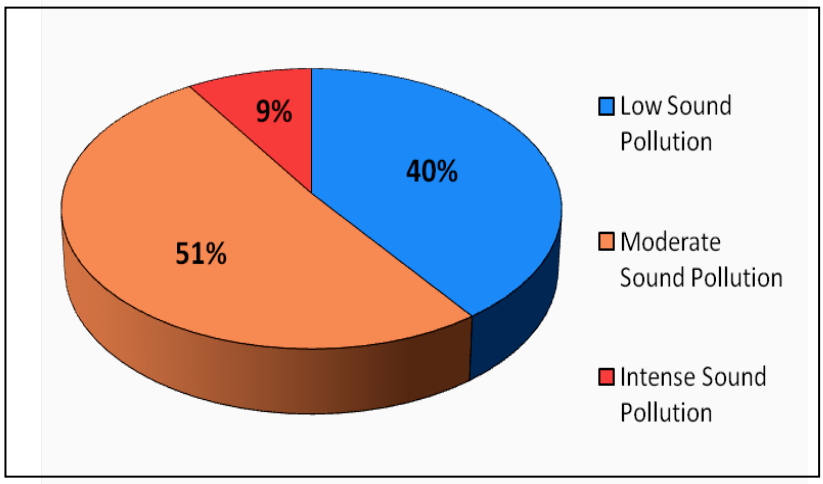


Figure 34. Intensity of sound pollution experienced by preeclamptic patients.

It was found that out of the 90 preeclamptic patients, 54 (60%) patients experienced moderate to intense sound pollution**.** On the contrary, 36 (40%) patients experienced low sound exposure**.** In cases of sound exposures, the generated sound exceeded the permissible limit of 40 dB, assigned by Department of Environment (DoE) of Bangladesh**.** The sources of intense sound pollution included intense sound of Govt. owned sugar mill, private sugarcane crusher mill, diesel driven power generator, hydraulic horn of some trucks and buses, movement of rail car with whistle, etc**.** Therefore, sound pollution might be another risk factor of preeclampsia**.**

C) Water Pollution: In 2000, British Geological Survey (BGS, UK) in collaboration with Department of Public Health Engineering (DPHE, Bangladesh) made an extensive groundwater survey in Bangladesh (n=3,540)**.** Merging their data sets (BGS/DPHE, 2001) with the preeclamptic patients' geographical locations, 15 metal concentrations of the drinking water (n=40) were found**.** The distribution of the metals in the drinking water is presented in the following Box-and-Whisker Plots (Figure 35) (using SPSS)**.**

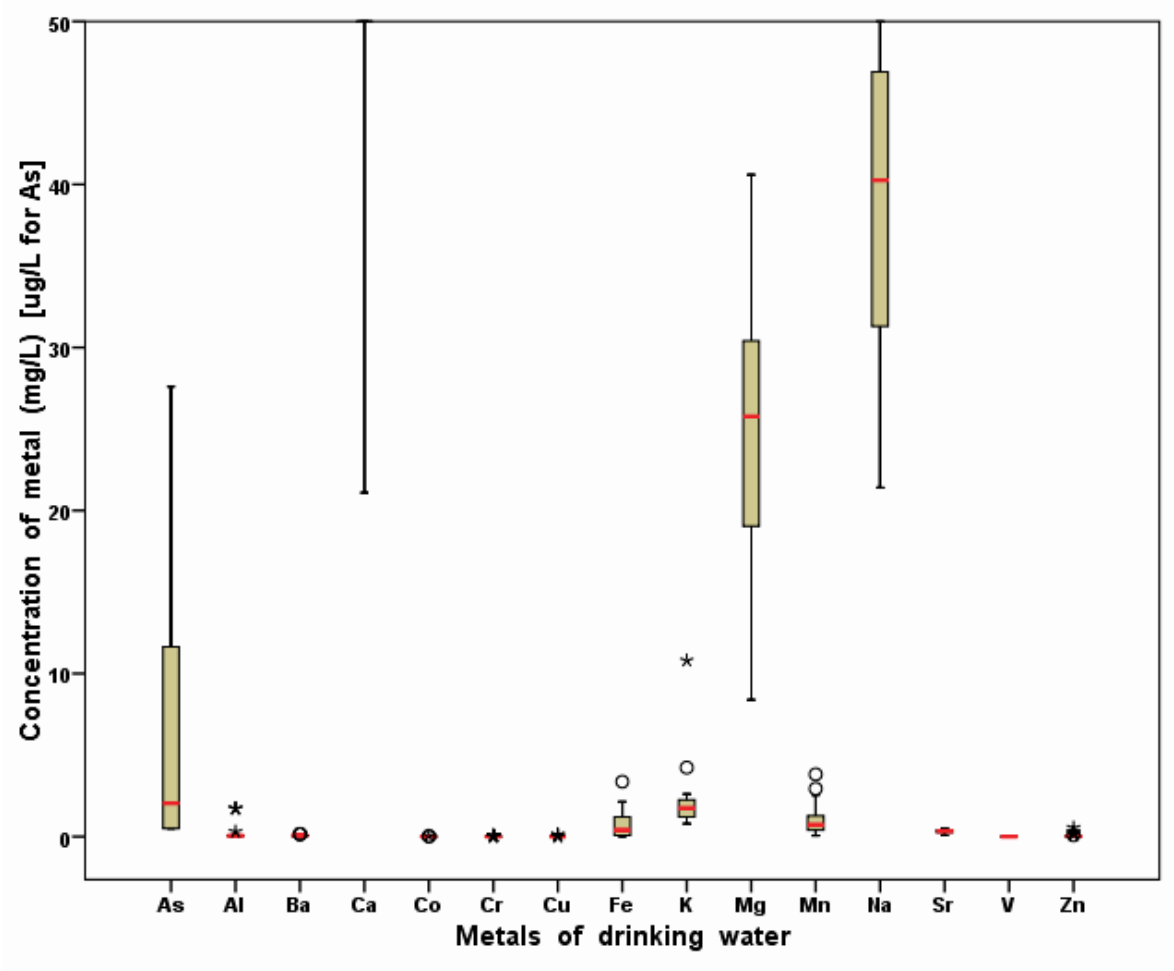


Figure 35. Box-and-Whisker plots for fifteen metals in the drinking water**.** [(▁) indicates median; lower and upper box boundaries 25th and 75th percentiles of each distribution; Whiskers as vertical lines ending in horizontal lines at the largest and smallest observed values; (*) indicates outside value and (^{O}) far outside value**.** Calcium concentration is out of the scale**.**]

The statistical analysis of the metals in drinking water along with the one-sample T-test are provided in Tables 15 and 16**.**

Table 15. Statistical analysis of the metals in drinking water**.**

	As (ug/L)	Al (mg/L)	Ba (mg/L)	Ca (mg/L)	Co (mg/L)	Cr (mg/L)	Cu (mg/L)	Fe (mg/L)	K (mg/L)	Mg (mg/L)	Mn (mg/L)	Na (mg/L)	Sr (mg/L)	V (mg/L)	Zn (mg/L)
WHO Std	10	0.2	0.7	-	0.1	0.05	2	0.3 - 1.0	-		0.1	50	-	-	3
Bd Std	50	0.2	0.01	75	-	0.05	1	0.3	12	30 - 35	0.1	200	-	-	5
No. of Obs.	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Max	164	1.72	0.165	148	0.056	0.064	0.118	3.37	10.8	40.6	3.82	60.7	0.524	0.008	0.54
Min	0.5	0.01	0.013	21.1	0.001	0.002	0.001	0.014	0.8	8.39	0.057	21.4	0.09	0.002	0.008
Mean	14.78	0.18	0.07	93.76	0.01	0.01	0.01	0.68	1.96	24.63	0.94	38.92	0.32	0.00	0.06
Std. Error of Mean	5.74	0.07	0.00	5.33	0.00	0.00	0.00	0.12	0.25	1.35	0.12	1.61	0.02	0.00	0.02
Median	2.05	0.05	0.07	95.45	0.00	0.00	0.01	0.40	1.75	25.77	0.73	40.25	0.33	0.00	0.02
Std. Deviation	36.33	0.45	0.03	33.69	0.01	0.02	0.02	0.73	1.59	8.53	0.79	10.20	0.10	0.00	0.10
Variance	1320.12	0.20	0.00	1135.24	0.00	0.00	0.00	0.53	2.53	72.84	0.62	103.98	0.01	0.00	0.01
Skewness	3.75	3.30	1.39	-0.29	4.62	2.61	4.27	1.57	4.62	-0.39	1.82	0.13	-0.41	0.80	3.55
Kurtosis	13.85	9.47	2.55	-0.57	24.36	6.15	17.17	3.30	25.42	-0.73	4.24	-0.75	0.14	-0.92	14.13

Table 16. One-sample T-test of the parameters.

	Test Value = 0					
	t	df	*P* value Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
As	2.573	39	0.014	14.784	3.164	26.404
Al	2.550	39	0.015	0.180	0.037	0.323
Ba	14.309	39	0.000	0.071	0.060	0.081
Ca	17.599	39	0.000	93.755	82.979	104.530
Co	4.505	39	0.000	0.006	0.003	0.009
Cr	3.614	39	0.001	0.009	0.004	0.014
Cu	3.490	39	0.001	0.013	0.006	0.021
Fe	5.848	39	0.000	0.675	0.441	0.908
K	7.808	39	0.000	1.964	1.455	2.472
Mg	18.252	39	0.000	24.623	21.900	27.359
Mn	7.586	39	0.000	0.943	0.692	1.195
Na	24.139	39	0.000	38.919	35.658	42.180
Sr	20.785	39	0.000	0.321	0.289	0.352
V	12.028	39	0.000	0.004	0.003	0.004
Zn	3.596	39	0.001	0.056	0.025	0.089

Comparison of the data with WHO guideline values (Table 15; WHO, 2017) reveals that Arsenic (As), Calcium (Ca), Magnesium (Mg), Iron (Fe) and Sodium (Na) concentrations in the patients' drinking water were comparatively high. The higher values of Ca and Mg indicate that the waters were hard. This along with elevated level of Fe might favor constipation. Na might assist in developing mild hypertension. The metalloid arsenic (As) has been classified as a human carcinogen of Group 1 by International Agency for Research on Cancer (IARC, 2012). The observed high level of arsenic in drinking water (here maximum concentration was 164 μg L^{-1}) might facilitate several adverse health effects. It was reported that arsenic causes acute lethality to chronic effects including vascular diseases, hypertension, cancer, hyperpigmentation, genotoxicity, diabetes mellitus, repeated abortions, stillbirth, preeclampsia, etc. (WHO, 2016; USEPA 2001). Therefore, safe drinking water is a concern for preeclamptic patients.

5.12 Mental Stress of the Preeclamptic Patients

Mental Stress of the studied preeclamptic mothers was estimated based upon 25 questionnaires (Annex 2), suggested by Canadian National Health Association (2012). Out of the 90 preeclamptic patients, 63 (70.00%) patients were under high mental stress and 22 (24.44%) under very high mental stress (Figure 36). On the contrary, only 5 (5.56%) patients had moderate mental stress. No preeclamptic patients were found to have less or without mental stress. Thus high mental pressure should induce hypertension and hence it is a potential risk factor for preeclampsia.

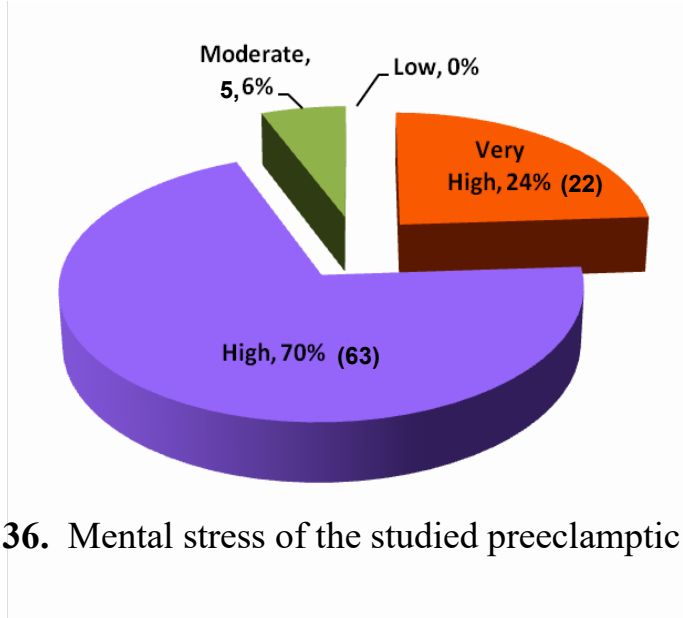


Figure 36. Mental stress of the studied preeclamptic patients.

Zhang *et al.* (2013) found that mental stress was associated with an increased risk of gestational hypertension (OR, 1.26; 95% CI, 1.00-1.59; P = 0.047) and preeclampsia (OR, 1.49; 95% CI, 1.27-1.74; P < 0.001). They also found that the work stress (OR, 1.50; 95% CI, 1.15-1.97; P = 0.003) and anxiety or depression (OR, 1.88; 95% CI, 1.08-3.25; P = 0.02) were positively associated with risk of preeclampsia. The present findings are in accordance with the results of Zhang *et al.* (2013).

5.13 Previous Gynecological and Obstetrical Histories of the Preeclamptic Patients

The previous gynecological and obstetrical histories of the preeclamptic patients are discussed below**:**

A) Patients' Period: In the present study it was found that the preeclamptic patients' first period was in the range of 11-15 years, averaging 12**.**9 years**.** Before being pregnant, 85**.**45% patients' period was regular; whereas only 5**.**5% irregular**.** The maximum and minimum bleeding duration was 3 and 8 days respectively, of which 5-6 days were more frequent**.** Most of the patients experienced low or moderate pain during period duration**.**

B) Previous Pregnancy: Most of the patients (number - 52; percentage -57**.**78) became pregnant earlier**.** Among the previously pregnant mothers, about 20% had their children**.** It was reported that most women with a history of gestational hypertension who experienced a subsequent hypertensive pregnancy will experience gestational hypertension again (median of 21%, range 8–47%); far fewer will experience their recurrence as preeclampsia (median of 4%, range 1–6%) (Zhang *et al.*, 2001; Hjartardottir *et al.*, 2006; Andersgaard *et al.*, 2012; Magee *et al.*, 2014)**.** It is to be noted that multiple gestations are also a risk factor for preeclampsia (Magee *et al.*, 2014)**.**

C) Previous Delivery Type: Out of the 52 previously pregnant women, 29 (55.55%) patients had the Normal Vaginal Delivery (NVD) and 13 (24.45%) had Cesarean Section (C/S) delivery. But 10 (20.00%) patients had the case of abortion. The distribution of the delivery types is shown in Figure 37, depicting that NDV > C/S (Cesarean section) > Abortion.

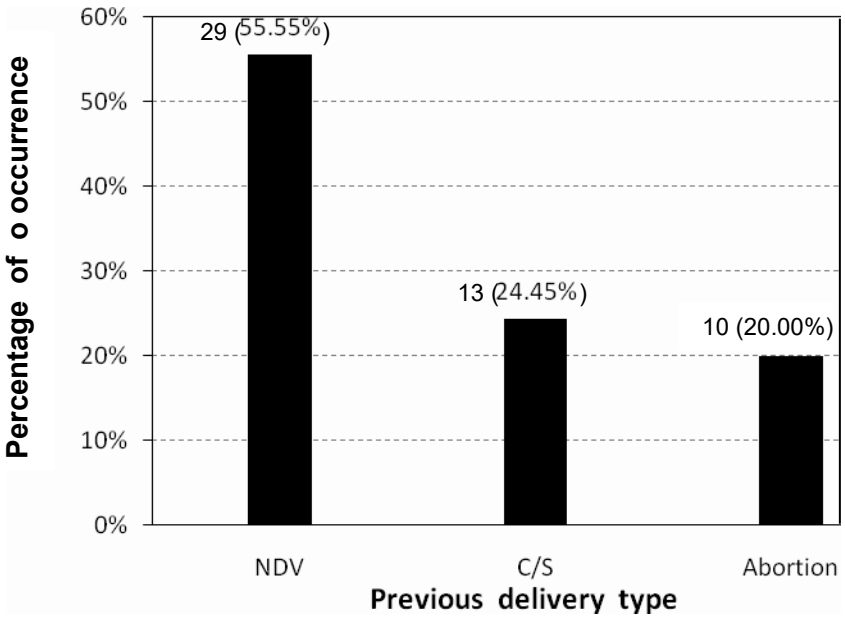


Figure 37. Distribution of previous delivery among the preeclamptic patients.

D) Previous Complications of Mothers and Infants: The main previous complications of the pregnant mothers (other than this one) included preeclampsia, eclampsia, excess post-partum hemorrhage and secondary infection. The principal complications of their infants were asphyxia, dyspnea and peri-natal death.

E) Previous Contraception Methods: Prior to be pregnant, the current preeclamptic pregnant mothers used several contraception methods. The order of the methods are as follows: Pill 43 (47.78%) > Barrier 19 (21.11%) > Natural 18 (20.00%) > Others 10 (11.11%) (Figure 38). Norplant and injection were included in others. Although excessive uses of steroid contained pills are not good, one-half of the women used it.

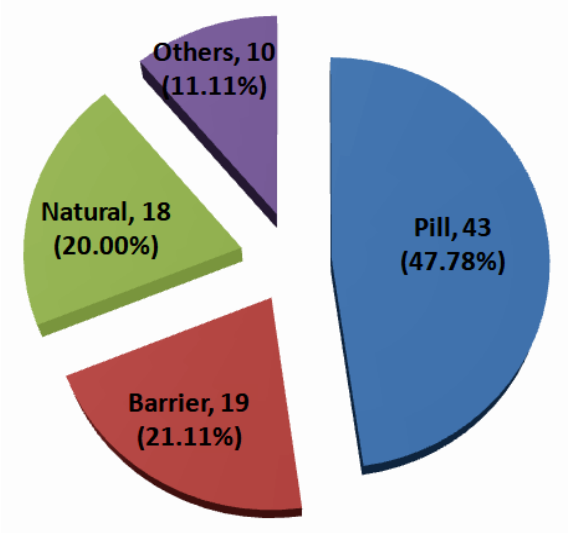


Figure 38. Previous contraceptive methods among the preeclamptic patients.

5.14 Past Medical, Surgical and Family History

The past medical and family histories of the current preeclamptic patients are mentioned below:

- The 15% of the patients had no significant *past medical history*. The remaining 85% had past medical history of chronic constipation, ashma, blood transfusion, UTI, hypertension, liver disease, diabetes and previous preeclampsia. No patient performed PAP or Memo test.

- The 60% patients had no record of *past surgical history*. Appendisectomy, DE&C (Dilatation, Evacuation and Curettage), MR (Menstrual Regulation), left Salphingo-oophorectomy and previous C/S occurred for other cases.
- The 17% patients have no *Past Family History*. But 83% patients have previous history of parent(s), brother/sister, uncle/aunt and grandfather. The principal family history include: Hypertension > Diabetes > Heart disease > Preeclampsia > Cancer.

5.15 Complications of the Preeclamptic Patients

A variety of complications were observed among the preeclamptic patients. Among the major complications, severe edema alone represents 44%, whereas headache and neck pain 19%, edema and hyperacidity 17%, lower abdominal and chest pain 12%, edema and vomiting 5% and blurring of vision 3% (Figure 39).

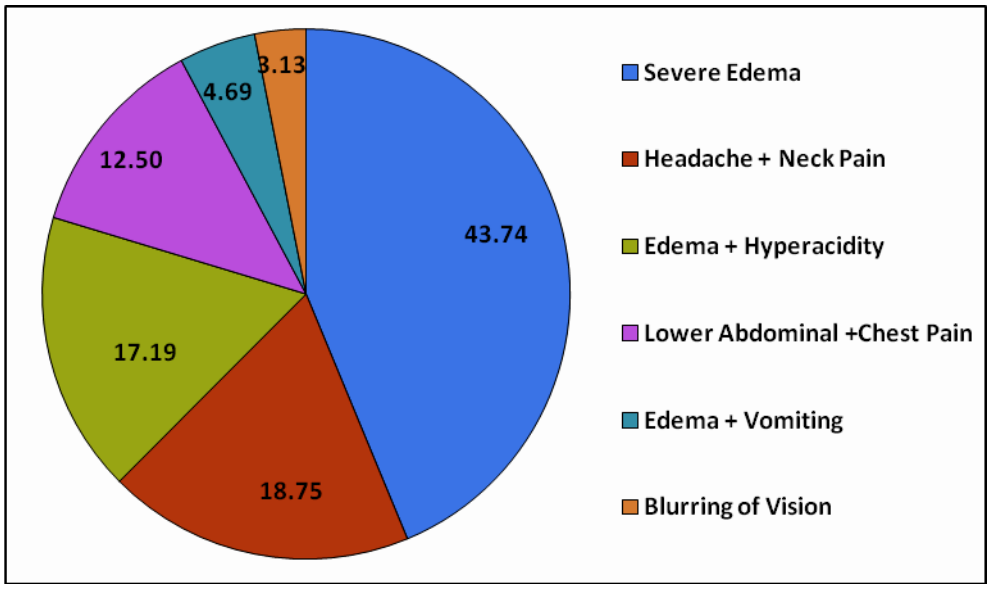


Figure 39. Complication of the preeclamptic patients.

Ngowa *et al.* (2015) found that in Cameroon, Eclampsia (12.14%), abruptio placentae (11.21%) and hypertensive retinopathy (7.47%) were the most frequent maternal complications (Table 17).

Table 17. Maternal complications of severe preeclampsia in Cameroon (Ngowa *et al.*, 2015).

Maternal complications	n	%
Eclampsia	13	12.14
Hypertensive retinopathy	8	7.47
CVA	3	2.80
HELLP syndrome	2	1.86
Acute renal failure	2	1.86
Abruptio placenta	12	11.21
DIC	1	0.93
Post-partum hemorrhage	7	6.54
Severe anemia	6	5.60
Severe ascitis	1	0.90
Maternal death	2	1.86

CVA: cerebral vascular accident; HELLP: DIC: disseminated intravascular coagulation.

5.16 Blood Pressure Pattern of Preeclamptic Patients

The preeclamptic patients' blood pressure fluctuated fairly, but remained in higher level. The highest blood pressure was found as 210/140 for the patient of 40 weeks gestation. For extreme cases, here B.P. 5, deliveries (either C/S or NVD) were performed. It was generally found that after delivery, the patients' B.P. fell down. But the trend was not uniform. The results are shown in Table 18.

Table 18. Blood pressure of preeclamptic patients before and after delivery.

Admission (wk)	Time of Delivery	B.P. 1	B.P. 2	B.P. 3	B. P. 4	B. P. 5
38+	Before C/S	160/120	140/90	200/120	180/110	180/110
	After C/S	160/100	150/95	150/100	160/100	140/90
40	Before C/S	165/100	160/100	200/120	180/130	210/140
	After C/S	180/130	200/120	170/110	160/100	150/95
32	Before NDV	160/110	150/110	160/110	160/110	180/110
	After NVD	160/100	150/100	140/95	140/90	130/90
37	Before C/S	130/95	140/100	150/110	150/120	180/110
	After C/S	170/140	190/120	150/100	140/100	130/90
38+	Before C/S	130/100	140/100	170/100	180/120	160/100
	After C/S	160/95	140/100	140/100	140/90	130/90
40	Before C/S	140/95	160/100	180/120	200/120	200/120
	After C/S	160/120	160/100	140/100	150/90	140/90
39	Before NDV	140/90	140/100	150/120	140/100	160/120
	After NVD	160/100	150/100	130/95	130/100	130/90

5.17 Bio-chemical Investigations of the Preeclamptic Patients

The bio-chemical investigations played a very vital role for proper diagnosis of the pregnant mothers for preeclampsia. The preeclamptic patients' bio-chemical investigations mainly comprised of hematological tests such as Hemoglobin, Platelet count, Random blood sugar (R.B.S.), Blood urea, Serum creatinine and Serum uric acid. The urinary tests included Albumin, Red blood cell (R.B.C.) and Pus cell. For severe preeclamptic patients, SGPT, Serum bilirubin, Serum Electrolyte tests were performed. The bio-chemical investigation findings are reported in the following Box-and-Whisker plots (Figure 40).

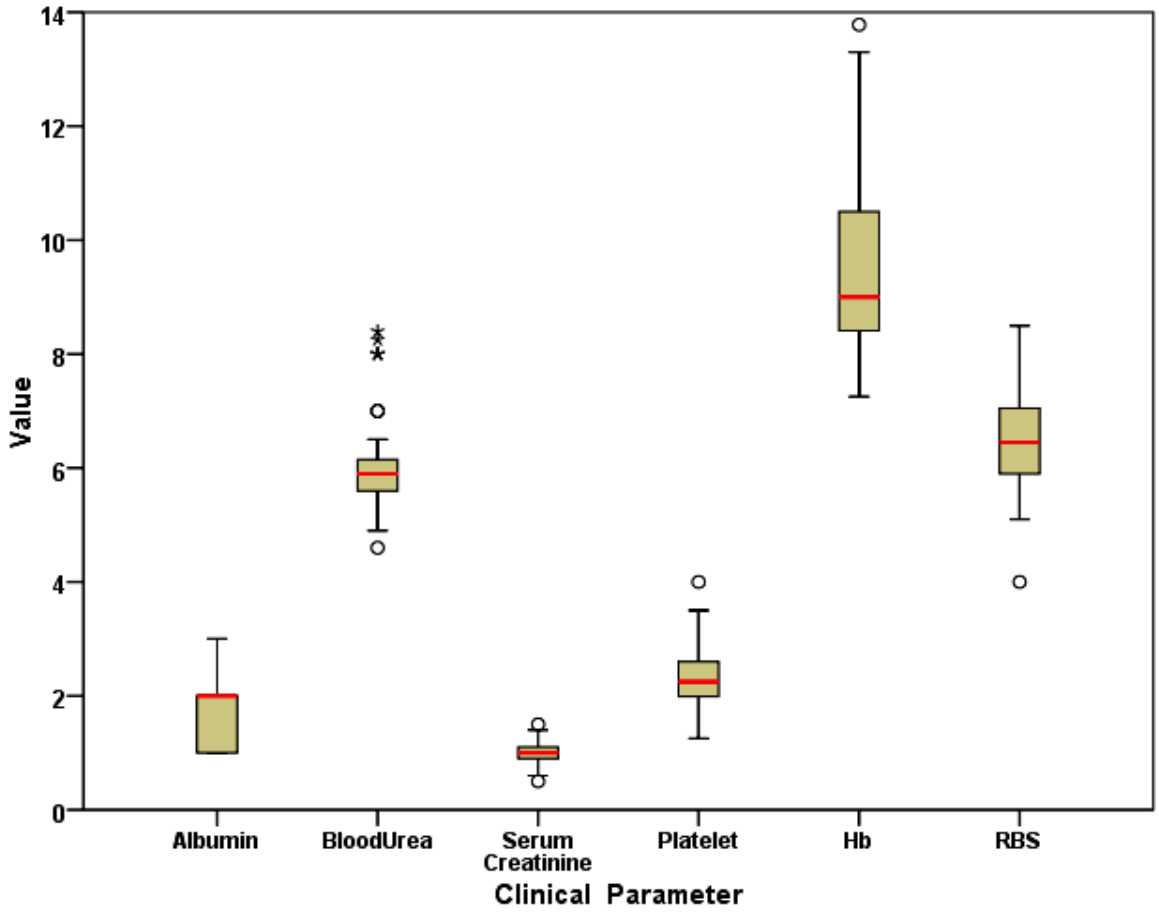


Figure 40. Box-and-Whisker plots for main bio-chemical investigations. [(–) indicates median; lower and upper box boundaries 25th and 75th percentiles of each distribution; Whiskers as vertical lines ending in horizontal lines at the largest and smallest observed values; (*) indicates outside value and (^{O}) far outside value. The Platelet count values would be multiplied by 100,000]

Serum Albumin test is a liver function test that measures the amount of this protein (albumin) in the clear liquid portion of the blood that was generated by liver. The increase in plasma volume that occurs during pregnancy leads to hemodilution and decreases the serum protein concentration (Blackburn and Loper, 2007). Lower values of serum albumin (average 1.54 g/dL) were observed among all the preeclamptic mothers (Table 19). Zannat *et al.* (2016) found average serum albumin values as 3.57 and 3.31 in 1st and 3rd trimester of pregnancy in Dinajpur of Bangladesh.

Table 19. Bio-chemical Investigation reports of the patients.

Test	Unit	Normal Values[§]	Values Obtained				Comparison of mean with normal value
			n	Min – Max	Mean	Median	
Albumin (Serum)	g/dL	3.1 – 5.1	90	1.0 – 3.0	1.54	2.00	Lower values
Blood Urea	mmol/L	2.5 – 7.1	55	4.6 – 8.4	5.92	5.80	Slight lower values
BUN[‡]	mg/dL	7 – 20	55	13 – 24	17	16	Slight lower values
Serum Creatinine	mg/dL	0.4 – 0.8	90	0.50 – 1.65	1.05	1.00	Slight higher values
Platelet Count	$10^3/mm^3$	174–391	69	124 – 400	236	250	Lower values
Hemo-globin	g/dL	11.6–13.9	73	6.63 – 13.78	9.02	8.70	Fairly lower values
R.B.S.	%	6.10	40	4.00 – 8.50	6.47	6.45	Slightly elevated
SGPT	U/L	3 – 30	10	12 – 100	41	36	Higher values
Serum Bilirubin	mg/dL	0.10–1.10	07	0.40 – 3.50	1.01	0.70	Slight lower values

[§] values are for pregnant women (Abbassi-Ghanavati *et al.*, 2009; Perinatology. 1016); [‡] BUN stands for blood urea nitrogen and was estimated by using the conversion factor of 0.357.

In the present investigation, the mean and median values of serum urea (n=55) of the preeclamptic mothers were found to be 5.92 and 5.80 mmol/L respectively. Comparison with normal value of 2.5 – 7.1 mmol/L revealed that the observed values were slightly lower. The estimated blood urea nitrogen (BUN) values were correspondingly lower (mean and median of 17 and 16 mg/dL).

Asamiya *et al.* (2009) found that in Japan there were significant negative relationships between the blood urea nitrogen (BUN) level and the birth weight or gestational age in the latter cohort. A birth weight equal to

or greater than 1,500 g or a gestational age equal to or exceeding 32 weeks corresponded to BUN levels of 48–49 mg/dl or less (Figure 41). It was reported (Zar *et al.*, 2011) that after delivery the serum urea or BUN level adjusted to normal values.

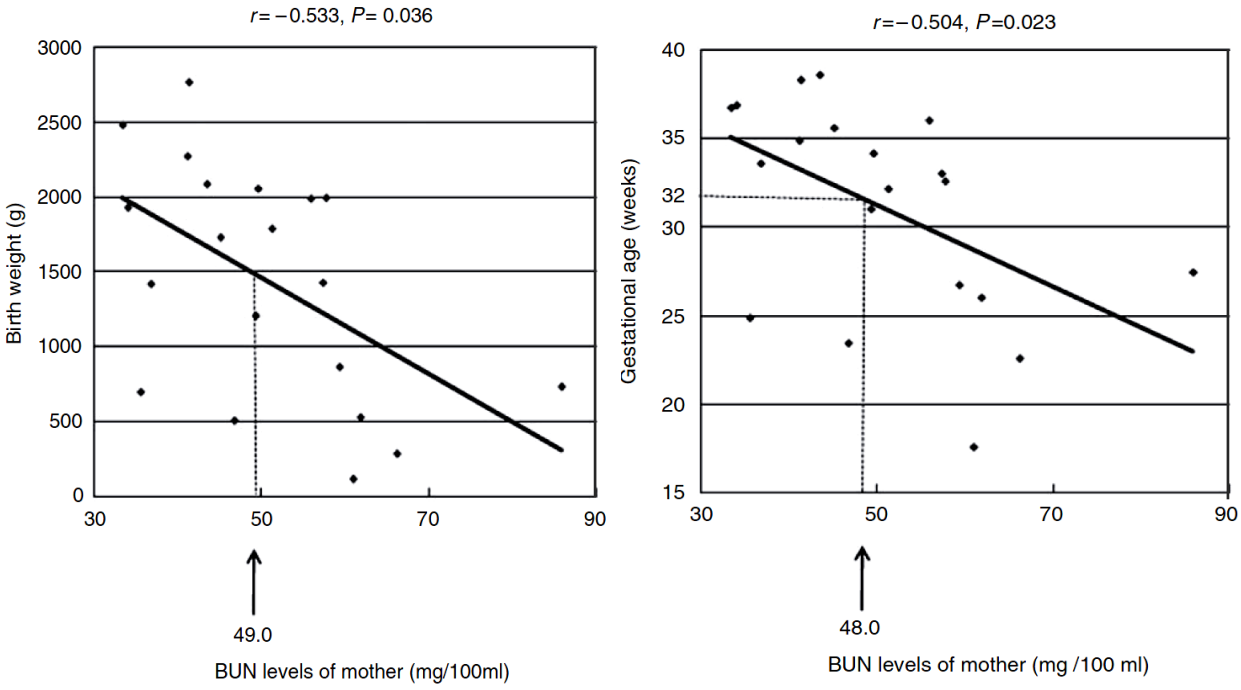


Figure 41. Relationships of maternal blood urea nitrogen (BUN) level with birth weight and gestational age (Asamiya *et al.*, 2009).

The physiologic increase in GFR during pregnancy normally results in a decrease in concentration of serum creatinine, which falls by an average of 0.4 mg/dL to a pregnancy range of 0.4 to 0.8 mg/dL. The observed relatively higher values of serum creatinine (n=90; more than 0.8 mg/dL) [Table 18] suggested intravascular volume contraction or renal involvement in preeclampsia.

In the present study, the mean and medium values of platelet count of the pregnant women were 236,000 and 250,000 per cubic mm of blood

respectively. Some common causes of low platelets during pregnancy include gestational thrombocytopenia, preeclampsia, HELLP syndrome, immune thrombocytopenic purpura (ITP). Our observed relative lower values of platelet count threw light on the presence of mild preeclampsia.

It is to be noted that low platelet count might be due to systemic lupus erythematosus, lupus anticoagulant, HIV infection, B_{12} deficiency, hyperthyroidism, massive transfusion, prosthetic heart valves, thrombotic thrombocytopenic purpura (TTP), sepsis, disseminated intravascular coagulation (DIC), hypersplenism, hemolytic uremic syndrome, hereditary thrombocytopenias, leukemia, aplastic anemia and drugs (heparin, zidovudine, sulfonamides, trimethoprim-sulfamethoxazole, sulfonamides, valproic acid, phenytoin , digitalis, ranitidine, cimetidine, ampicillin, penicillin, alpha-methyl dopa, ethanol, aspirin, acetaminophen, indocin) (Abbassi-Ghanavati *et al.*, 2009). But some causes of an increased platelet count include myeloproliferative disease (essential thrombocytosis, chronic myelogenous leukemia, polycythemia vera, myelofibrosis) and reactive thrombocytosis (postpartum ,hemorrhage, iron deficiency, inflammation, decreased or absent spleen function).

The fairly lower values of hemoglobin for the patients (n=73), mean and median values of 9.02 and 8.70 g/dL respectively, reflected that the concerned preeclamptic mothers are highly anemic. It is known that the greater the severity of the anemia during pregnancy, the greater is the risk of preeclampsia, preterm delivery, low birth weight (LBW) and stillbirth. Ali *et al.* (2011) found 13.8% Stillbirth, 20.7% low birth weight, 11.5% preterm birth for severly anemic preeclamptic patients in Sudan.

The random blood sugar (R.B.S.) levels of the preeclamptic mothers were slightly elevated to the target value of 6.10% (HbA1c). This means that the patients were not under diabetics and this is important to ensure the best chance of a successful pregnancy.

Preeclampsia is associated with significant morbidity and mortality for mother and baby but it resolves completely postpartum. In preeclampsia hypervascularization & vasoconstriction of liver leads to liver cell injury and alteration of cell membrane permeability. Damage to the cell allows intracellular enzyme to leak into the blood leading to elevated liver enzymes like SGOT, SGPT (serum glutamic pyruvic transaminase) and SAP (Girling *et al.*, 1997). The observed higher values of serum SGPT (mean and median of 41 and 36 U/L respectively compared with normal values 3 – 30 U/L) were found to be associated with preeclampsia.

Bilirubin is a known antioxidant and as such is associated with a reduced risk of cardiovascular and respiratory disease. The observed low levels of bilirubin were associated with women diagnosed with preeclampsia.

5.18 Drug Administration for the Preeclamptic Patients

The preeclamtic patients were confirmed based upon patients' B.P., edema and serum albumin along with physiological complications and other laboratory investigations. The pregnancy duration of the patients was within range of 35-38 gestational weeks. After being confirmed, they were subjected to treatment in the Hospital/Clinic. Proper drug management was a part of it, which is discussed below.

Drugs for B.P. management: Tab Sardopa, Tab Nifin, Tab Labeta
Drugs for pleeclamptic fit management: Inj Nalepsin ($MgSO_4$)
Drug for tension management: Inj Barbit

The raw materials or active ingredients of the drugs Sardopa, Nifin, Labeta, Barbit were Methyldopa, Nifedipine, Labetalol and Phenobarbital. Their structural formulae are represented in Figure 8. The dose and duration of the drugs were dependent upon the severity of preeclampsia and gestational duration of the patients.

5.19 Timing and Mode of Delivery

It was observed that the maximum and minimum gestational ages during delivery were 40 and 32 weeks respectively, averaging 37 weeks. The distribution of the preeclamptic patients based upon the gestational age during delivery ($P < 0.001$) is shown in Figure 42.

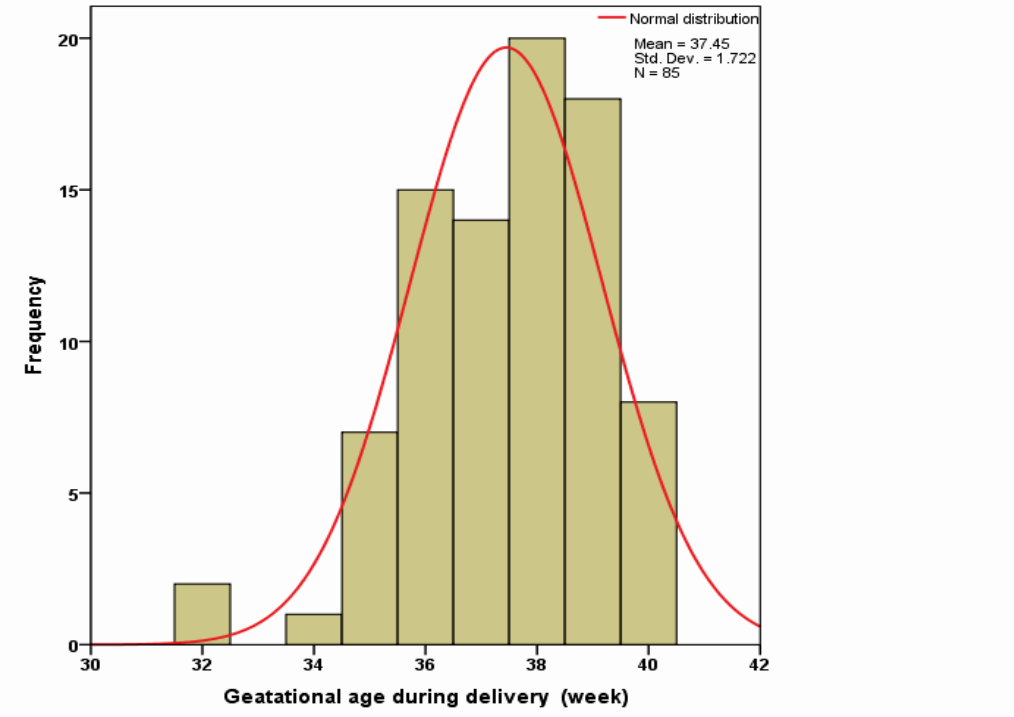


Figure 42. Distribution of delivery (based on gestational age) of the patients.

The delivery pattern for the preeclamptic mothers admitted into RMCH is represented in the following Figure**.** Obviously, about three-fourths of the patients' deliveries were made by C/S, while the rest by NVD**.** Two patients were released for being admitted into other hospital**.**

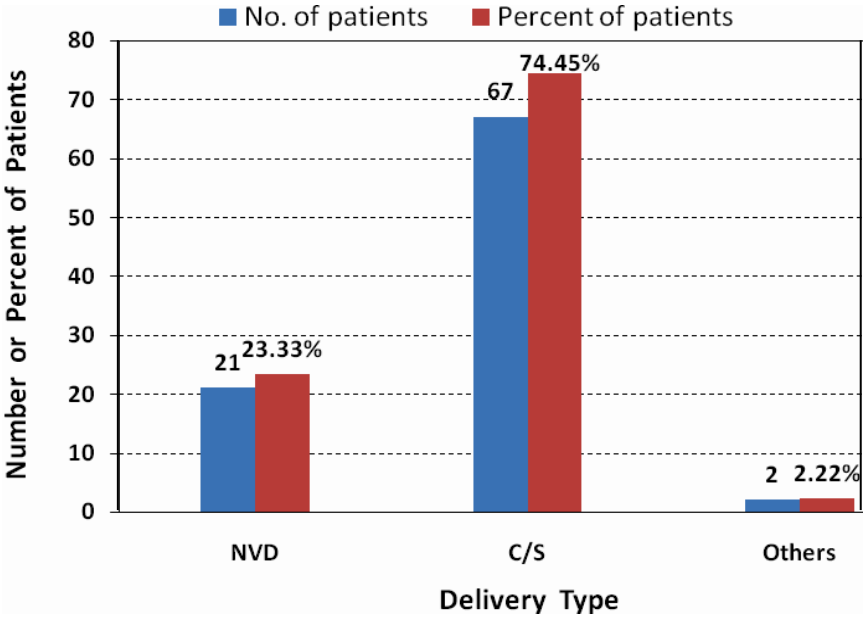


Figure 43. Delivery pattern of the preeclamptic patients**.**

Ye *et al.* (2014) found that in China Cesarean Section (C/S) accounted for 78**.**27% for mild preeclampsia, 86**.**27% for severe preeclampsia and 94**.**23% for eclampsia**.** The frequency of caesarian section in Iran was reported as 45**.**8% (Zibaeenezhad *et al.*, 2010)**.** Other researchers (Coppage and Polzin, 2002; Pádua *et al.*, 2010) found the C/S prevalence as 58%-79%**.** The present prevalence rate was within the range**.**

5.20 Maternal and Neonatal Outcome

It was generally observed that after delivery, the concerned mothers' health conditions were good, whereas new-born infants' conditions were bad. But before delivery, the mothers' conditions were bad (Figure 44).

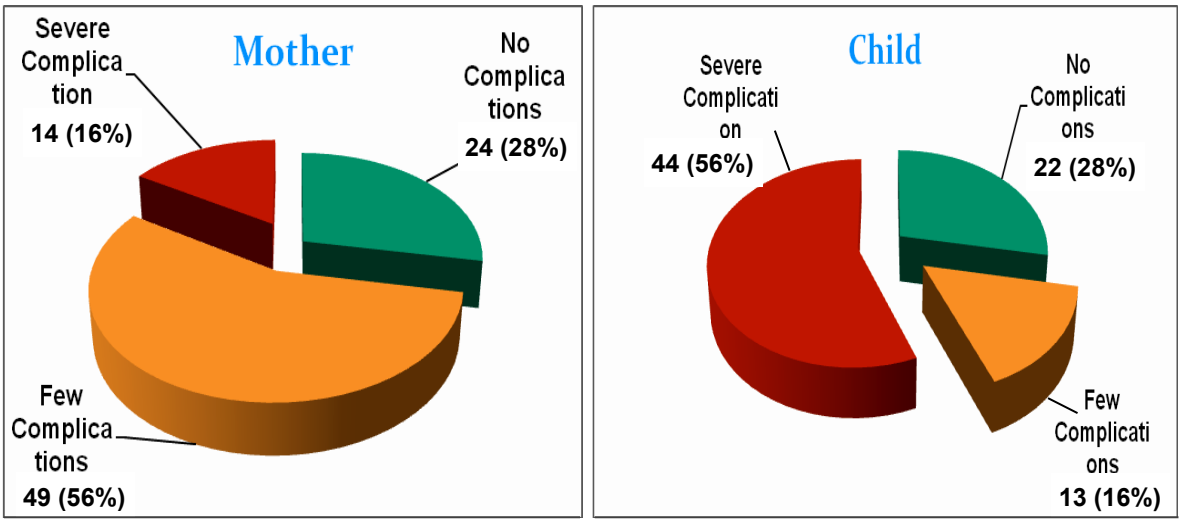


Figure 44. The conditions of the mother and the child after delivery.

The details of both maternal health after giving birth and new-born infants are enlisted in Table 19.

It was found that one patient out of 88 had died after giving birth (maternal morbidity rate of 1.14%), which was probably due to conversion to severe eclampsia or HELP syndrome. It was interesting to note that her female infant (weighing 2.0 kg) was in good condition. Only one case of twin-pregnancy was recorded. The new-born infants were both female and in good health conditions having weights of 3.0 and 2.5 kg. With regard to maternal heath after giving births, 27.59% had no complications, whereas 49 (56.32%) had few/mild complications. On the contrary, only 14 (16.09%) had severe complications (Table 20).

Table 20. Conditions of the mothers and infants after delivery.

Factor	Number	Percentage
Maternal life status (n = 88)		
Alive	87	98.86%
Dead	01	1.14%
Maternal health status (n = 87)		
No complications	24	27.59%
With few complications	49	56.32%
With severe complications	14	16.09%
Neonatal gender (n = 88)		
Male	53	60.23%
Female	35	39.77%
Neonatal life status (n = 88)		
Alive	79	89.77%
Dead	09	10.23%
Neonatal health status (n = 79)		
No complications	22	27.84%
With few complications	13	16.46%
With severe complications	44	55.70%
Neonatal body weight (n = 79)		
Low birth weight (< 2.5 kg)	33	41.77%
Standard weight (≥ 2.5 kg)	46	58.23%

It was observed that male children dominated (53; 60.23%) over female children (35; 39.77%) in case of preeclamptic mothers. In the study, a total of 9 (10.23%) neonatal deaths were recorded out of 88 neonatal. Among the alive infants, 41.77% were premature having body weight of < 2.5 kg, while the rest (58.23%) were with standard health (≥ 2.5 kg). About 28% of the newly born infants had no complications, while 13 (16.46%) had few/mild complications. On the contrary, 44 (55.70%) had severe complications. Such complications included Asphyxia, IUGR, etc.

In China, similar findings were reported for neonatal outcomes (Ye *et al.*, 2014). Their data is presented in Table 21 for comparison purpose.

Table 21. Perinatal outcomes between women with and without HDP in China (Ye *et al.*, 2014).

Group	N	LBW (%)	Neonatal Asphyxia (%)	Perinatal Death (%)
GH	2091	214(10.23)	102(4.88)	44(2.10)
Mild Preeclampsia	949	159(16.75)	58(6.11)	11(1.16)
Severe Preeclampsia	2522	1134(44.96)	479(18.99)	206(8.17)
Eclampsia	53	40(75.47)	24(45.28)	5(9.43)
PSCH	222	93(41.89)	66(29.73)	31(13.96)
CHP	358	40(11.17)	31(8.66)	17(4.75)
With HDP	6195	1697(27.39)	760(12.27)	314(5.07)
Without HDP	108192	6167(5.70)	3689(3.41)	1456(1.35)
Total	114387	7864(6.87)	4449(3.89)	1770(1.55)
X2		4306.9	1230.0	533.1
P		<0.001	<0.001	<0.001

Many countries such as Cameroon (Ngowa *et al.*, 2015), Ghana (Adu-Bonsaffoh *et al.*, 2017), Ethiopia (Berhe *et al.*, 2018), USA (Kuklina *et al.*, 2009) have similar findings like our observations.

5.21 Morphological Changes of Placenta in Preeclampsia

The morphological changes of placenta in some preeclamptic mothers were examined with the help of Fluorescence Illuminating Motorized Inverted System Microscope. Keeping the experimental conditions as ……, we found that ……

Figure 45. Morphological changes of placenta in some preeclamptic mothers**.**

Table 13. Statistical analyses on some demographic data of the preeclamptic patients.

Variable	Unit	n	Range	Median	Mean ± SE	95% C.I.[a] for mean	Standard Deviation	Variance	Skewness	Kurtosis
Age	yr	90	16 – 40	25.00	26.34 ± 0.73	24.88 – 27.80	5.888	34.665	0.455	-0.575
Body weight	kg	90	45 – 82	62.00	26.34 ± 0.73	61.07 – 65.53	9.018	81.319	0.237	-0.369
Height	cm	90	127 – 167	152.00	26.34 ± 0.73	150.78 – 154.21	6.915	47.816	-1.546	3.336
BMI	$kg\ m^{-2}$	90	17 – 38	27.30	26.34 ± 0.73	26.16 – 28.45	4.610	21.248	0.290	-0.433
Education	–	90	0 – 18	10.00	26.34 ± 0.73	8.31 – 10.49	4.401	19.369	-0.182	-0.451
Monthly income	Tk	90	0 – 20,000	0.00	26.34 ± 0.73	492 – 2,185	3,418	1.168×10^{7}	4.158	18.682
Wealth	Tk	90	0 – 3,000,000	100,000	26.34 ± 0.73	149,930 – 407,916	520,580	2.710×10^{11}	3.713	15.700
Socio-economic Index	–	90	12 – 57	15.00	26.34 ± 0.73	19.30 – 24.98	11.467	131.496	1.283	0.575

[a] C.I. stands for Confidence Interval.

CHAPTER SIX :

CONCLUSIONS

6.1 CONCLUSIONS

Preeclampsia is a multi-system obstetrical disorder of unknown etiology in which a lot of risk factors are associated. World Health Organization (WHO, 2016) reviewed 129 studies covering 39 million women from 40 countries (2002–2010) and found the incidence of preeclampsia as 2.3% (4.6% using a model-based estimation). In some countries of Asia and Africa, the rates of preeclampsia are as high as 5–7%. Ten million women develop preeclampsia each year around the world. Worldwide about 76,000 pregnant women die each year from preeclampsia and related hypertensive disorders. And, the number of babies who die from these disorders is thought to be on the order of 500,000 per annum (Kuklina *et al.*, 2009; Preeclampsia Foundation, 2013). But the origin of preeclampsia is still elusive. With this view, the present study was conducted to address mainly the prevalence and the associated risk factors of preeclampsia. The main findings are summarized below:

It was found that the number of pregnant mother admitted into Rajshahi Medical College Hispital (RMCH) for delivery or obstructed complications was increased from 11,532 to 17,201 during the year 2013 to 2017. Consequently, the number of preeclamptic patients was also increased from 407 to 435. The average number of preeclamptic patients found in RMCH per year is 484 (during the last five years). This is equivalent to 3.21% of total pregnant mothers admitted into RMCH for delivery or with obstructed complications.

The rate of preeclampsia in pregnant women in Rajshahi region is decreasing with respect to time. This is probably due to increase in consciousness of the pregnant women and their attendants as well as the proper initiatives taken by the Government of Bangladesh. With the trend observed, it is forecasted that in the years 2020, 2023 and 2026 the preeclampsia incidence rate should be 2.02%, 1.30% and 0.58% respectively.

The age of the participating preeclamptic patients ranged from 16 to 40 years, with an average of 25.90 ± 0.65 years. The 69% of the preeclamptic patients were below the age of 29 years. About one-fourth of the preeclamptic mothers were below 20 years, whereas only 1% mother was at 40 years. This reflects that the youngest mothers are at high risk of preeclampsia.

Based upon the BMI values obtained, preeclamptic patients were classified as Underweight (< 18.5), Normal (18.5 – 24.9), Overweight (25 – 29.9) and Obese (≥ 30). It was observed that as the patients were more obese, the occurrence of preeclampsia was increased more. The health type order of the preeclamptic patients followed the order: Obese (40%) > Overweight (29%) = Normal (29%) > Underweight (2%). The gained weight for the pregnant women at 40 weeks gestation was 11.3 - 15.9 for normal, 6.8 - 11.3 for overweight and 5.0 - 9.1 for obese mother. The obese or overweight pregnant preeclamptic mothers were associated with some additional complications including severe edema, severe headache, vomiting, lower abdominal pain and hyperacidity.

In the present study, preeclamptic patients' had mainly A+, B+ or O+ blood groups. The prevalence of preeclampsia based on patients' blood grouping was as follows: A+ (39%) > B+ (33%) > O+ (24%) > AB+ (2%) = O– (2%). It is interesting to note that no preeclamptic patients had A–, B– and AB– blood groups and only 2% patients had very rare O– blood group.

The prevalence of graduate and masters level completed preeclamptic patients was found as 20%. The vulnerable preeclamptic patients were under matriculated (S.S.C.), which accounted for 66.67%. Thus, two-thirds of the patients completed education level 10. The 4.44% preeclamptic patients were also illiterate. This means that the preeclamptic patients were not very conscious about preventing preeclampsia.

Socio-economic Index (SEI) is a measure of social class, which was determined from patient's occupation, education, income level and wealth. It was found that out of 90 preeclamptic patients, 69 were within the SEI range of 10 – 30, whereas 21 were above the range. This means that about three-fourths of the concerned patients were of lower social class. The probable reasons included that the vulnerable patients were housewife having low income and wealth and were not properly educated.

In the study, out of the 90 preeclamptic patients, 80 (88.89%) were Muslims and 10 (11.11%) were Hindus, no Christians and Buddhists were found. 38 patients (42.22%) were from single families, whereas 52 (57.78%) from joint families. On the basis of patients' occupation, 80 (88.89%) patients were housewives, 6 (6.67%) were teachers and 4 (4.44%) were in other services. Regarding ethnicity all were local women, not migrated. Among the pregnant women, 55 (61.11%) were white, 12 (13.33%) were gray and 23 (25.56%) were black.

The pregnant women and their attendants were conscious about food habits and hence took more vegetables and fruits. HIES surveys found Bangladeshi intake rate of pulse, fish, meat, egg, milk, vegetables and fruits as 14.3, 49.5, 19.0, 7.2, 33.7, 166.1 and 44.7 gram per capita per day respectively. Most of the patients exceeded the amounts. But they took less amount of required liquid, which is essential for expanding extra-cellular space and amniotic fluid. The 51.11% of total women took drinking water below the recommended 2.2 L/day.

Most of the patients' living rooms were within 15 feet from kitchen. Only 10% patients had good room ventilation, while the remaining 90% patients had either moderate or poor room ventilation. Combination of distance of living room from kitchen and room ventilation reveals that the preeclamptic patients were subjected to moderate CO_2 exposure.

It was found that 78.89% of the preeclamptic patients' living rooms were below 50 ft from the nearest roads. The value was 84.44% for 100 ft distance. Therefore, it is reasonable that they would experience sound pollution. In order to understand it, the traffic conditions and other potential sources of sound pollutions were considered. The sources of intense sound pollution included intense sound of Govt. owned sugar mill, private sugarcane crusher mill, diesel driven power generator, hydraulic horn of some trucks and buses, movement of rail car with whistle, etc. Combination of these two factors revealed that 60% of the preeclamptic patients experienced moderate to intense sound pollution.

Comparison of the obtained data with WHO guideline values reveals that Arsenic (As), Calcium (Ca), Magnesium (Mg), Iron (Fe) and Sodium (Na) concentrations in the patients' drinking water were comparatively high. The higher values of Ca and Mg indicate that the waters were hard. This along with elevated level of Fe might favor constipation. Na might assist in developing mild hypertension. The metalloid arsenic (As) has been classified as a human carcinogen of Group 1 by IARC. The observed high level of arsenic in drinking water (here maximum concentration was 164 $\mu g\ L^{-1}$) might facilitate several adverse health effects of acute lethality to chronic effects including vascular diseases, hypertension, cancer, genotoxicity, hyperpigmentation, diabetes mellitus, repeated abortions, stillbirth, preeclampsia, etc. Therefore, safe drinking water is a concern for preeclamptic patients.

The study reveals that 94% of the preeclamptic mothers were under high or very high mental stress, of which 24% were very high and 70% were high. High mental pressure should induce hypertension and hence it is a potential risk factor for preeclampsia.

The previous gynecological and obstetrical histories of the 90 preeclamptic patients were investigated. The preeclamptic patients' first period was in the range of 11-15 years, averaging 12.9 years. Before being pregnant, 85.45% patients' period was regular; whereas only 5.5% irregular. The maximum and minimum bleeding duration was 3 and 8 days respectively, of which 5-6 days were more frequent. Most of the patients experienced low or moderate pain during period duration. The 58% of the patients became pregnant earlier, of which 20% had their children. In this case, the delivery order was as follows: NDV > C/S > Abortion. After giving birth, 48% of them used steroid contained pills as contraceptive method.

The 60% patients had no record of past surgical history. Appendisectomy, DE&C (Dilatation, Evacuation and Curettage), MR (Menstrual Regulation), left Salphingo-oophorectomy and previous C/S occurred for other cases. The principal family history include: Hypertension > Diabetes > Heart disease > Preeclampsia > Cancer.

Among the major complications of the preeclampsia, severe edema alone represents 44%, whereas headache and neck pain 19%, edema and hyperacidity 17%, lower abdominal and chest pain 12%, edema and vomiting 5% and blurring of vision 3%. It was observed that the patients' blood pressure fluctuated fairly, but remained in higher level. The highest blood pressure was found as 210/140 for the patient of 40 weeks gestation. For extreme cases, here B.P. 5, deliveries (either C/S or NVD) were performed. It was generally found that after delivery, the patients' B.P. fell down. But the trend was not uniform.

The bio-chemical investigations played a very vital role for proper diagnosis of the pregnant mothers for preeclampsia. Serum Albumin test, a liver function test, measures the amount of albumin in clear liquid portion of blood that was generated by liver. Fairly lower values of serum albumin (average 1.54 g/dL) in all the studied preeclamptic mothers were observed. This indicates the increase in plasma volume that occurs during the pregnancy leading to hemodilution. The observed slight lower values of serum urea (average 5.92 mmol/L) and blood urea nitrogen (BUN) (average 17 mg/dL) reflected higher possibility of low-birth weight (LBW) neonatal output. The observed relatively higher values of serum creatinine (> 0.8 mg/dL) suggested intravascular volume contraction or renal involvement in preeclampsia. The relative lower values of platelet count (average 2.34 million/mm^3) threw light on the presence of mild preeclampsia. The fairly lower values of hemoglobin (average of 9.02 g/dL) reflected that the studied preeclamptic mothers are highly anemic. Thus, they were under greater risk

of preeclampsia, preterm delivery, LBW and stillbirth**.** The random blood sugar (R.B.S.) levels of the preeclamptic mothers were not very elevated (6**.**10%) reflecting that the patients were not under diabetics and this was important to ensure the best chance of a successful pregnancy**.**

The preeclamtic patients were confirmed based upon patients' B.P., edema and serum albumin along with physiological complications and other laboratory investigations**.** After being confirmed, they were subjected to treatment in the Hospital along with drug administration (mentioned below)**:**

*Drugs for B.P. management***:** Tab Sardopa (*Methyldopa*), Tab Nifin (*Nifedipine*), Tab Labeta (*Labetalol*)

*Drugs for pleeclamptic fit management***:** Inj Nalepsin ($MgSO_4$)

*Drug for tension management***:** Inj Barbit (*Phenobarbital*)

It was observed that the maximum and minimum gestational ages during delivery were 40 and 32 weeks respectively, with the average of 37 weeks**.** About three-fourths of the patients' deliveries were made by C/S, while the rest by NVD**.** Two patients were released for being admitted into other hospital**.**

It was generally observed that after delivery, the concerned mothers' health conditions were good, whereas new-born infants' condition were bad**.** But before delivery, the mothers' conditions were bad**.**

It was found that one patient out of 88 had died after giving birth (maternal morbidity rate of 1.14%), which was probably due to conversion to severe eclampsia or HELLP syndrome. It was interesting to note that her female infant (weighing 2.0 kg) was in good condition. Only one case of twin-pregnancy was recorded. The new-born infants were both female and in good health conditions having weights of 3.0 and 2.5 kg. With regard to maternal heath after giving births, 28% had no complications, whereas the remaining (72%) had either mild or severe complications.

We observed that male children dominated (about 60%) over female children (about 40%) in case of preeclamptic mothers. In the study, a total of 9 neonatal deaths were recorded out of 88, representing 10.23% of total. Among the alive infants, 41.77% were premature having body weight of < 2.5 kg, while the rest (58.23%) were with standard health (≥ 2.5 kg). About 28% of the newly born infants had no complications, while the rest (72%) were under mild or severe complications. Such complications included Asphyxia, IUGR, etc.

In most cases, the placentae of the preeclamptic patients were found as oval in shape. The examination of morphological changes of placenta in some preeclamptic mothers reveals the development of endothelial cell body in moderate to mild extent, probably due to deposition of subendothelial fibrinoid. But normal pregnant women exhibited endotheliosis to lesser extent.

CHAPTER SEVEN :

RECOMMENDATIONS

7.1 RECOMMENDATIONS

In order to get rid of life threatening preeclampsia, early detection, taking proper prompt treatment and necessary preventing measures are essential. On the basis of the findings of the present study, the followings are recommended to reduce the possibility and frequency of preeclampsia as well as its proper management among the hypertensive pregnant women:

1) *Use of Calibrated Sphygmomanometer*: The elevation of systolic and diastolic blood pressures of the pregnant mothers is the prime concern for preeclampsia. Therefore the patients' B.P. must be monitored with properly calibrated Sphygmomanometer. The wrong B.P. measurement is life threatening to severe preeclamptic patients. It is suggested that in this case, the calibrated instrument might be kept reserved for this purpose alone.

2) *Following the Proper Techniques of B.P. measurement*: Accurate B.P. measurement is a challenging one. Blood pressure measurement in pregnancy should follow the same standardized technique as outside pregnancy and the 'Best Practice Points' suggested by Magee *et al.* (2016). Please refer to section 4.9 of this book.

3) *Cross-checking the Accuracy of Laboratory Investigation Reports*: Many hospitals and diagnostic centers use different methods and reagents for laboratory analysis. Only those reports should be acceptable that follow the standard guidelines and authorized by Directorate General of Health.

Prior to providing reference for the bio-chemical tests, the obstetrician must know the concerned centers' calibration procedures and use of non-expiry and high-quality reagents. This is very important for preeclamptic patients, because identification of preeclampsia is solely based on it. Any questionable report should also be cross-checked with other recognized diagnostic center.

4) *Proper Monitoring of the Patients*: It was generally observed that the frequency of preeclamptic patients was high in winter season than in other seasons. Since the incidence rate of preeclampsia in Bangladesh is normally high (about 5%), therefore proper monitoring of the patients at that time should be ensured.

5) *Taking More Amount of Water*: In the present study, it was found that more than 51% of the patients took less than 2.2 L of drinking water per day, which was below WHO recommended level. But pregnant women require additional fluid replacement to ensure that foetal needs are met, as well as providing for expanding extra-cellular space and amniotic fluid. That's why, the preeclamptic patients should take more safe drinking water.

6) *Taking Balanced Foods*: Obese preeclamptic mothers were found to associate with some additional complications like severe edema, severe headache, vomiting, lower abdominal pain and hyperacidity. So they are advised to take more balanced diets (e.g., more protein diets, vegetables, fruits and milk) rather than junk food to meet additional food requirement.

7) *Less Exposed to CO_2 and Noise Pollution*: If the patient visit in 1st or 2nd trimester of her pregnancy, she should be advised to shift in such a room of her house that is more distant kitchen and has well ventilation. This will keep her less exposed to CO_2. More the room should have low sound impact or sound-proof. Both the factors will exert low stress of environmental pollution on the patient. So the patients are advised not to be exposed to CO_2 and noise pollution.

8) *Taking Safe Drinking Water*: If the drinking water of the pregnant mother contains toxicants such as arsenic (As), lead (Pb), Cadmium (Cd), etc. (also act as carcinogens), then many unexpected events/disease like vascular diseases, severe hypertension, cancer, genotoxicity, hyperpigmentation, diabetes mellitus, repeated abortions, stillbirth, severe preeclampsia, etc. might happen. Moreover, if the water is hard, it may induce constipation. Therefore, the drinking water parameters should be checked at regional DPHE (Department of Public Health Engineering) Lab, if there is scope. Alternatively, the patient should be advised to drink less contaminated deep aquifer water (Tara pump, pipeline water) instead of Tube-well water (originated from shallow aquifer).

9) *Changing Intension for C/S*: It was observed that three-fourth of preeclamptic mothers' delivery were performed by C/S. Since C/S causes additional complications, the obstetrician should facilitate NVD where possible.

CHAPTER EIGHT :

LIMITATIONS

OF THE STUDY

8.1 LIMITATIONS

Since the present study was on hypertensive pregnant women experiencing preeclampsia and the fetal outcomes, ensuring *Quality Control* in each step of data collection was the prime concern**.** It was always remembered that a significant error might be introduced in primary data gathering**.** But in a very few cases, it was not possible to attain the desired level of maximum accuracy for some instrumental and methodical constrains**.** These were treated as the limitations of the study, which are mentioned below**:**

1. In the study, the impacts of environmental pollution (namely, air, water and sound pollutions) on preeclamptic patients were estimated based upon the concerned patients' statement**.** This was qualitative, not quantitative**.** To understand the contaminant level of the patients drinking water, the data (n=3,542) of British Geological Surveys of Bangladeshi aquifer water were utilized**.** For accurate information site-specific surveys and sample analyses should be performed, although this was huge tasks and beyond the scope**.** However, the gathered data with the concerned patients' parents and attendants were cross-checked**.**

2. A few bio-chemical investigations of the preeclamptic patients were performed in other laboratories outside RMCH**.** This was due to patients' own interests or in case of technical problems or to save some time for severe preeclamptic patients**.** However, those laboratories that ensured quality control in sample analysis were recommended**.**

3. Mental Stress exposed on preeclamptic patients based on Canadian Mental Health Association prescribed questionnaire was estimated**.** It contained 25 Yes/No questions (Appendix 2)**.** Sometimes the patients lost their patience at the end and were then not very attentive**.** However, motivational statements worked then**.**

4. No data were available other than Rajshahi Medical College Hospital (RMCH), since the concerned other private Hospitals/Clinics did not keep the records of preeclamptic patients properly**.**

CHAPTER NINE :

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9.1 REFERENCES

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Chapter Ten :

Appendices

Appendix - 1

QUESTIONNAIRE ON "PRE-ECLAMPSIA"

Serial No.: ☐ **Date:** dd / mm/ yyyy

Interviewer's Name: Dr. ……

Interviewer's Designation: ……

Interviewer's Institution: ……

……

Name of Patient Attending Hospital / Clinic:

……

Address of Patient Attending Hospital / Clinic:

……

Particulars

Patient's Name: ……

Patient's Address: ……

Patient's Signature: ……

Patient's Mobile No.: ……

Patient's Husband/Father/Mother Mobile No.: . ……

2. Interviewer's Signature: …… **Date:** ……

DEMOGRAPHIC INFORMATION

Age: ☐ yr **Weight:** ☐ kg **Height:** ☐ ft ☐ in

***BMI*:** ☐ (Underweight ☐ Normal Weight ☐ Overweight ☐ Obesity ☐)

Ethnicity: White ☐ Gray ☐ Black ☐

Local ☐ Immigrant ☐ Tribe ☐ Other ☐ (_____)

Religion: Muslim ☐ Hindu ☐ Christian ☐ Buddhist ☐ Other ☐

Education: 0 >0-5 Primary >5-10 Secondary >10-12 Higher Secondary >12-16 Bachelor >16-18 Masters >18

Occupation: _____ Full Time ☐ Part Time ☐

Income Level: Tk. _____ / month

Wealth: Name: _____ Amount: Tk. _____

Living Situation: Joint Families ☐ Single Family ☐

Socioeconomic Index: _____ **Social Class:** _____

FOOD HABIT

Vegetarian ☐ Non-vegetarian ☐

Amount of Diet Taken per Day: Vegetables: _____g, Fruits: _____ g, Fish: _____ g, Milk: _____ mL, Fast Food: _____ g, Water: _____ mL.

Smoking / Alcohol / Drug Status: Non-smoker ☐ Smoker ☐ (_____ sticks/day)

Illicit Drug Use: No ☐ Yes ☐ (_____Name_____ ; _____Amount / Day_____)

Alcohol Use: No ☐ Yes ☐ (_____Name_____ ; _____Amount / Day_____)

ENVIRONMENTAL IMPACT STUDY

CO_2 Exposure: **Serum CO_2 Level:** _____ m mol L^{-1}

Room: Spacious ☐ Congested ☐ Distance from kitchen: ____ft Ventilation: _____

Drinking Water Parameters: **pH:** _____ **Electrical Conductivity:** _____ mS

As: _____ µg L^{-1} **Pb:** _____ µg L^{-1} **Cd:** _____ µg L^{-1} **Fe:** _____ µg L^{-1}

Sound Pollution: **Distance from Road:** ____ ft **Traffic Condition:** _____

Any Source of additional sound: _____

GYNAECOLOGICAL HISTORY

Age at first period: _____ years

Period Type: Regular ☐ Interval: _____ days

Irregular ☐ Interval: _____ to _____ days (e.g., 12 to 60)

Bleeding Duration: _____ days

Is Pain associated with Period? No ☐ Yes ☐ (Intense / Moderate / Low)

OBSTETRICAL HISTORY

Pregnancy / Abortion / Ectopic Pregnancy History:

Have you ever been pregnant ? No ☐ Yes ☐ (Fill in the following form)

Year	Place of Delivery / Abortion	Duration Pregnancy	Delivery Type	Complication (Mother & Child)	Child's Health & Condition

Birth Control Method Before Pregnancy:

Natural ☐ Pill ☐ Barrier ☐ Norplant ☐ IUCD ☐

Does Bleeding / Spotting Occur After Intercourse? No ☐ Yes ☐

Do You Take Fertilization Pill Before Pregnancy? No ☐ Yes ☐

Vaginal Bleeding in Pregnancy (≥ 5 days): No ☐ Yes ☐

(If Yes, Gestation: _____ week, Severity: _____ , Duration: _____)

Complications During Pregnancy: No ☐ Yes ☐

(Details: _____)

PAST MEDICAL HISTORY

(Put Tick where necessary)

☐ Arthritis	☐ Gall Stone	☐ Bronchitis
☐ Diabetes (Diet/Pill/Insulin)	☐ Liver Disease	☐ Polycystic Ovarian Syndrome
☐ High Blood Pressure	☐ Thyroid Disease	☐ UTI
☐ Heart Disease	☐ Asthma	☐ HIV
☐ Blood Transfusion	☐ Previous Pre-eclampsia	☐ Other (_____)

PAP Smear Test: No ☐ Yes ☐ (Result: Normal / Abnormal _____)

Mammography Test: No ☐ Yes ☐ (Result: Normal / Abnormal _____)

Current Medications:	Name	Dose / Day	Duration
1.			
2.			
3.			
4.			

Past Surgical History:	Name	Year
1.		
2.		
3.		

FAMILY HISTORY

☐ Diabetes ☐ Heart Disease ☐ High B.P.

☐ Cancer (Ovarian / Endometrial / Breast / Colon / Lung) ☐ Pre-eclampsia

☐ Other (_____)

If Yes, Whom: _____ _____

STRESS ESTIMATION

As per attached sheet

PHYSIOLOGICAL & CLINICAL PROFILE

B.P. Record, 1st Visit, With Additional Observations: (Gestational Scale on Week)

1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
15		**16**		**17**		**18**		**19**		**20**		**21**	**22**
23		**24**		**25**		**26**		**27**		**28**		**29**	**30**
31		**32**		**33**		**34**		**35**		**36**		**37**	**38**
39		**40**		**41**		**42**							

Edema Observed: No ☐ Yes ☐ (When: _____)

Special Notes:

Bio-clinical Investigations: (Mention Date and Result for two Examinations)

Albumin: _____ _____

Blood Urea: _____ _____

Serum Creatine: _____ _____

R.B.C: _____ _____

Platelet Count: _____ _____

CONFIRAMTION AND FOLLOW UP

Preeclampsia: No ☐ Yes ☐

(If Yes, Confirmed on: B.P. ☐ Edema ☐ Bio-chemical Investigations ☐)

Advice of Non-preeclamptic (Hypertensive) Patients:

1. Hospitalization (At ____ weeks gestation in _____)
2. Medical Treatment: a)
   b)
   c)
   d)
3. Follow up: _____

_____

Advice of Preeclamptic Patients:

1. Hospitalization (At ____ weeks gestation in _____)
2. Medical Treatment: a)
   b)
   c)
   d)
3. Follow up: _____

_____

OUTCOME

Year	Place of Delivery/Abortion	Duration Pregnancy	Delivery Type	Complication (Mother & Child)	Child		
					Sex	Birth weight	Present Health

Observation of Placenta: **Diameter:** Outer ____ cm Inner ____ cm

Length: ____ ft ____ in **Weight:** _____ kg (**Amniotic Fluid:** _____ L)

Cross-sectional and Peripheral Observations (with naked eye and Microscope)**:**

_____

_____

Appendix - 2

PATIENTS' CONSENT FORM

I, Mrs. ……, Father/Husband of ……..,
Address ……,
Age …….. years, hereby declare that I have participated in the research work entitled "*Prevalence of preeclampsia causing pregnancy complications and its associated risk factors among women in Rajshahi region*", conducted by **Sultana Nasima Alhter** (Ph.D. Fellow, Institute of Environmental Sciences, University of Rajshahi, Bangladesh)**.**

I have been explained clearly (in my own mother language Bengali) about the purpose and benefits of the study**.** I have been informed that through this research, there may have the possibility of new advancement in the field of Medical Sciences, particularly in diagnosis and treatment of preeclampsia**.** It is assured that all the information that I shall provide will be kept confidential; no name is needed to mention in the research paper and no mental or physical stress will be applied**.** Freedoms have given to me for the participation in the study or discontinue participation at any time without any prior notice**.**

I, being fully aware of, have agreed to contribute on voluntary basis**.** I also declare that I shall not demand any financial support for taking part in this research work**.** I have given my full consent voluntarily for inclusion of myself in the study as a subject**.**

Signature/Stamp Date**:** ……
Full Name**:**
Address**:**

Appendix - 3

রোগীর সম্মতিপত্র (বাংলায়)

আমি, মিসেস ……, পিতা/স্বামী……..,
ঠিকানা ……,
বয়স …….. বছর, এইমর্মে ঘোষণা করছি যে, **সুলতানা নাসিমা আখতার** (পি-এইচ,ডি ফেলো, ইন্সটিটিউট অব বায়োলজিক্যাল সায়েন্সেস, রাজশাহী বিশ্ববিদ্যালয়, বাংলাদেশ) কর্তৃক পরিচালিত গবেষণা কার্যক্রমে (শিরোনাম - *Prevalence of preeclampsia causing pregnancy complications and its associated risk factors among women in Rajshahi region*) অংশগ্রহণ করলাম।

আমাকে উক্ত গবেষণার উদ্দেশ্য ও সুবিধাসমূহ পরিষ্কারভাবে নিজ মাতৃভাষা বাংলায় ব্যাখ্যা করা হয়েছে। আমাকে জানানো হয়েছে যে, এই গবেষণার মাধ্যমে চিকিৎসা বিজ্ঞানে, বিশেষ করে প্রি-একলাম্পিসিয়ার রোগ সনাক্তকরণ ও চিকিৎসাক্ষেত্রে নতুন অগ্রগতির সম্ভাবনা রয়েছে। আমাকে আশ্বস্ড় করা হয়েছে যে, আমার দেয়া তথ্যাদির গোপনীয়তা বজায় রাখা হবে। এই গবেষণায় অংশগ্রহণে অথবা গবেষণা চলাকালে যে কোন মূহুর্তে কোন কারণ ব্যতিরেকে আমার অংশগ্রহণ প্রত্যাহার করার অধিকার সংরক্ষণ করলাম।

আমি, সজ্ঞানে, স্বেচ্ছায় অংশগ্রহণ করতে সম্মত হয়েছি। আমি আরও ঘোষণা করছি যে, এই গবেষণা কাজে অংশগ্রহণের জন্য আমি কোন আর্থিক সুবিধা দাবী করবো না। এই গবেষণাকর্মের বিষয় হিসাবে স্বেচ্ছাসেবার ভিত্তিতে অংশগ্রহণের জন্য আমি নিজে সম্পূর্ণ সম্মতি প্রদান করলাম।

স্বাক্ষর/টিপসই তারিখ: ……

পূর্ণ নাম:

ঠিকানা:

Appendix - 4: Online Parameter Estimation

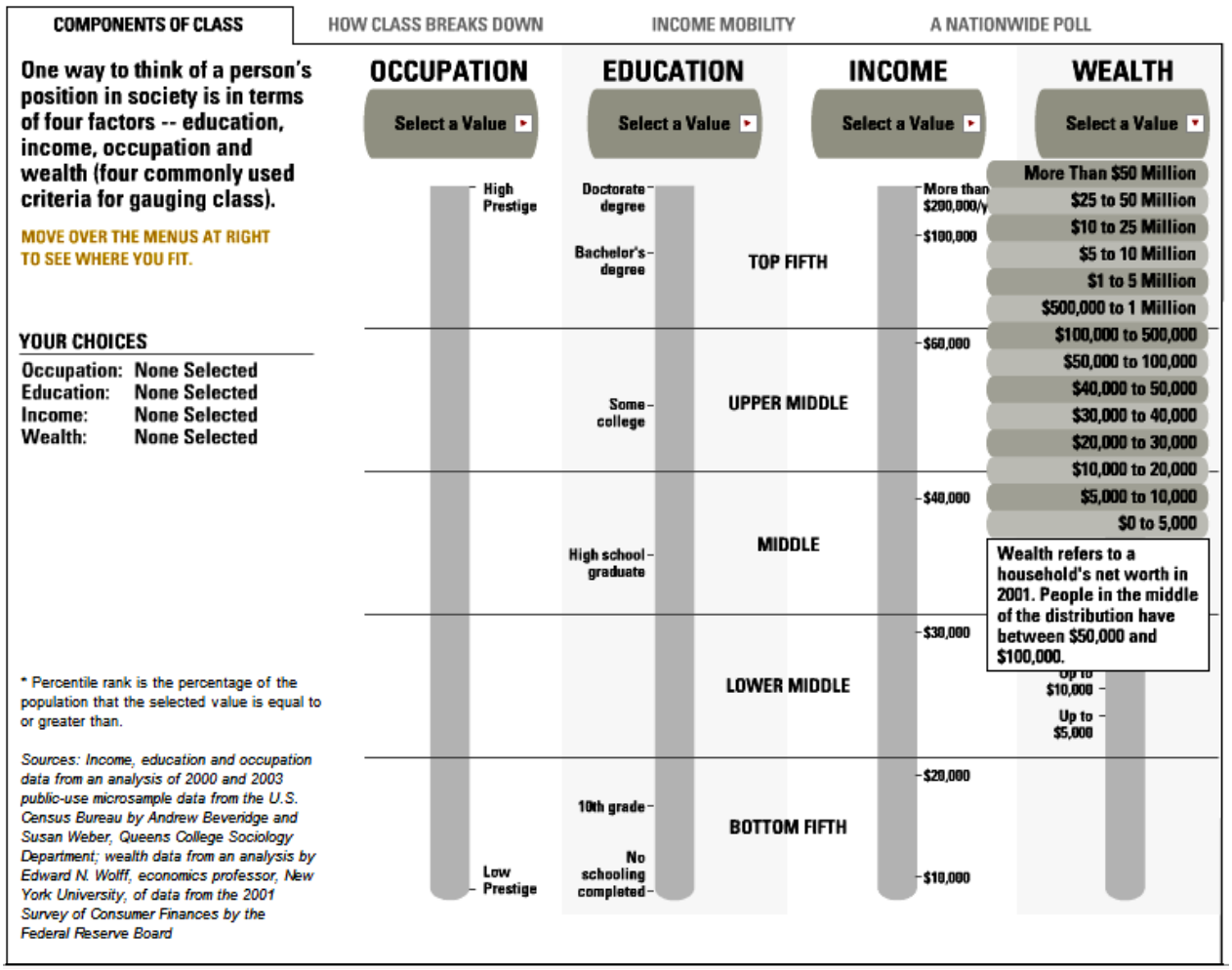
ONLINE STRESS ESTIMATION (Canadian Mental Health Association, 2012)

DO YOU FREQUENTLY:	YES	NO
Neglect your diet?	○	○
Try to do everything yourself?	○	○
Blow up easily?	○	○
Seek unrealistic goals?	○	○
Fail to see the humour in situations others find funny?	○	○
Act rude?	○	○
Make a 'big deal' of everything?	○	○
Look to other people to make things happen?	○	○
Have difficulty making decisions	○	○
Complain you are disorganized?	○	○
Avoid people whose ideas are different from your own?	○	○
Keep everything inside?	○	○
Neglect exercise?	○	○
Have few supportive relationships?	○	○
Use sleeping pills and tranquilizers without a doctor's approval?	○	○
Get too little rest?	○	○
Get angry when you are kept waiting?	○	○
Ignore stress symptoms?	○	○
Put things off until later?	○	○
Think there is only one right way to do something?	○	○
Fail to build relaxation time into your day?	○	○
Gossip?	○	○
Race through the day?	○	○
Spend a lot of time complaining about the past?	○	○
Fail to get a break from noise and crowds?	○	○

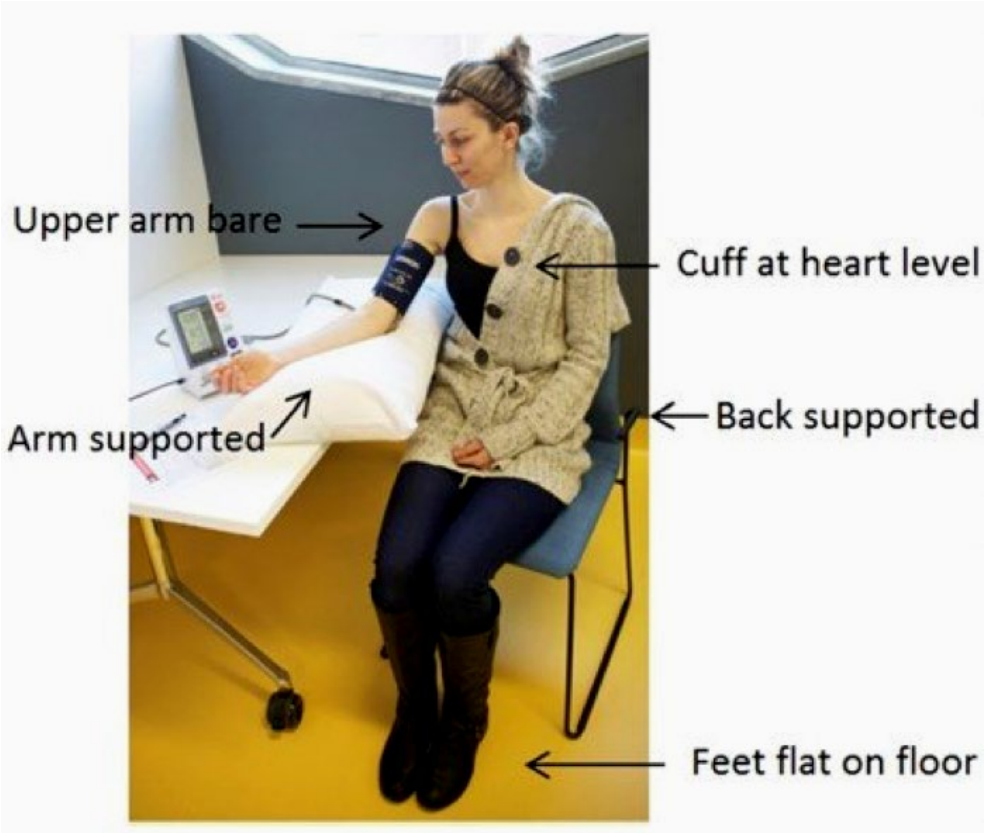
WHAT'S MY SCORE? Click this button to get your score

ONLINE SOCIOECONOMIC INDEX ESTIMATION

(Reference: The New York Times, 2018)



Appendix - 5: Correct Blood Pressure Measurement Procedure



(Reference: Desai, 2014)

Appendix - 6: Drinking Water Quality Parameters

[Adapted from British Geological Survey, UK; BGS, 2001]

Address	As (μg/L)	Al (mg/L)	B (mg/L)	Ba (mg/L)	Ca (mg/L)	Co (mg/L)	Cr (mg/L)	Cu (mg/L)	Fe (mg/L)
WHO Std	**10**	**0.2**	**2.4**	**0.70**	**-**	**0.1**	**0.05**	**2**	**0.3 - 1.0**
BD Std	**50**	**0.2**	**1.0**	**0.01**	**75**	**-**	**0.05**	**1**	**0.3**
Bagatipara, Natore	0.8	0.07	0.10	0.087	128.0	0.003	0.002	0.008	1.16
Paba, Rajshahi	24.3	0.07	0.10	0.113	106.3	0.004	0.004	0.008	1.25
Bagha, Rajshahi	2.4	0.06	0.09	0.076	115.6	0.004	0.02	0.008	0.41
Rajpara, Rajshahi	1.7	0.01	0.02	0.063	148.0	0.001	0.005	0.001	0.02
Niamotpur, Naogaon	0.5	0.01	0.10	0.048	61.6	0.003	0.002	0.008	0.86
Iswardi, Pabna	9.0	0.04	0.02	0.097	130.0	0.008	0.002	0.008	0.61
Chuadanga S,Chuadanga	27.6	0.04	0.03	0.153	98.2	0.056	0.064	0.008	1.40
Shibgang, C. Nawabganj	24.4	0.04	0.10	0.150	116.5	0.003	0.004	0.010	0.81
Halsa, Kusthia	0.5	0.04	0.02	0.058	104.0	0.008	0.020	0.008	0.02
Nachole, C. Nawabganj	0.5	0.30	0.10	0.068	80.6	0.003	0.002	0.008	3.37
Natore Sadar, Natore	11.6	0.08	0.1	0.165	91.5	0.003	0.002	0.008	2.14
Pabna Sadar, Pabna	6.0	0.06	0.03	0.063	116.0	0.008	0.002	0.008	0.22
Gomostapur, C.Nawabganj	6.0	0.04	0.02	0.050	59.1	0.008	0.020	0.008	0.17
Kansat, C. Nawabganj	6.0	0.04	0.02	0.043	105.0	0.008	0.002	0.008	0.08
Charghat, Rajshahi	0.5	0.06	0.10	0.079	135.0	0.003	0.002	0.008	0.038
Mohadevpur, Noagoan	1.6	0.01	0.10	0.013	21.1	0.003	0.002	0.008	0.65
Tanore, Rajshahi	0.5	0.04	0.10	0.069	59.1	0.003	0.002	0.008	0.08
Mohanpur, Rajshahi	58.2	0.06	0.10	0.069	120.0	0.003	0.002	0.008	0.53
Manda, Naogaon	164.0	0.01	0.10	0.078	30.8	0.003	0.002	0.008	1.36
Puthia, Rajshahi	0.5	0.06	0.10	0.072	146.0	0.003	0.002	0.008	0.059
Godagari, Rajshahi	6.0	0.04	0.01	0.039	64.0	0.008	0.020	0.060	0.04
Bagmara, Rajshahi	14.3	0.11	0.10	0.080	88.4	0.003	0.002	0.008	1.42

Continued…

Address	K (mg/L)	Li (mg/L)	Mg (mg/L)	Mn (mg/L)	Na (mg/L)	P (mg/L)	Si (mg/L)	SO_4 (mg/L)	Sr (mg/L)	V (mg/L)	Zn (mg/L)
WHO Std	**-**	**-**		**0.1**	**50**	**-**	**-**	**250**	**-**	**-**	**3**
BD Std	**12**	**-**	**30 - 35**	**0.1**	**200**	**0**	**-**	**400**	**-**	**-**	**5**
Bagatipara, Natore	2.4	0.012	29.1	1.10	31.5	0.2	19.4	9.8	0.343	0.002	0.248
Paba, Rajshahi	2.3	0.008	29.4	1.49	35.1	0.3	21.7	0.6	0.322	0.003	0.025
Bagha, Rajshahi	2.0	0.010	32.1	1.32	34.4	0.1	18.6	0.6	0.425	0.003	0.047
Rajpara, Rajshahi	1.7	0.004	36.2	2.54	40.7	0.2	16.1	14.9	0.476	0.002	0.020
Niamotpur, Naogaon	1.2	0.007	15.6	0.16	33.7	0.1	23.7	1.1	0.256	0.002	0.030
Iswardi, Pabna	1.2	0.003	34.8	1.10	31.1	0.2	12.1	9.2	0.430	0.006	0.008
Chuadanga S,Chuadanga	10.8	0.948	22.8	0.45	24.5	0.3	16.1	8.3	0.271	0.006	0.113
Shibgang, C. Nawabganj	4.2	0.012	32.8	0.72	25.3	0.15	16.3	10.0	0.420	0.002	0.020
Halsa, Kusthia	1.5	0.005	28.0	0.49	28.1	0.2	19.7	0.9	0.332	0.006	0.009
Nachole, C. Nawabganj	1.2	0.010	20.4	0.54	38.9	0.15	21.5	1.2	0.318	0.002	0.540
Natore Sadar, Natore	2.6	0.008	24.7	0.59	21.4	0.2	16.0	13.6	0.230	0.003	0.053
Pabna Sadar, Pabna	0.9	0.005	30.4	0.36	50.9	0.2	17.2	1.9	0.411	0.006	0.019
Gomostapur, C.Nawabganj	0.8	0.007	10.5	0.179	43.4	0.2	23.9	11.0	0.242	0.006	0.009
Kansat, C. Nawabganj	1.2	0.007	31.4	0.97	35.1	0.2	15.4	6.5	0.342	0.006	0.010
Charghat, Rajshahi	1.6	0.008	35.3	1.28	30.0	0.1	18.5	0.9	0.415	0.003	0.023
Mohadevpur, Noagoan	0.8	0.007	8.4	0.54	23.9	0.3	27.8	6.4	0.092	0.002	0.031
Tanore, Rajshahi	2.1	0.004	22.5	0.72	60.7	0.1	29.8	64.7	0.458	0.002	0.016
Mohanpur, Rajshahi	1.7	0.004	37.1	2.94	47.8	0.3	18.3	0.2	0.524	0.003	0.031
Manda, Naogaon	1.9	0.008	10.7	0.73	57.0	0.6	20.2	1.5	0.118	0.002	0.036
Puthia, Rajshahi	2.4	0.013	29.8	1.28	41.3	0.1	21.6	2.6	0.358	0.002	0.014
Godagari, Rajshahi	0.9	0.009	12.5	0.06	41.2	0.2	22.4	15.9	0.288	0.006	0.022
Bagmara, Rajshahi	1.5	0.006	20.4	0.79	26.4	0.1	18.2	0.2	0.303	0.002	0.084

Appendix - 7: Relationship Between Qualitative and Quantitative Scales (Gilbert, 2013)

A) GRADING OF PROTEINURIA IN URINE:

Dipstick Result	Amount of Protein in Urine ($g\ L^{-1}$)
Trace	0.01
1 +	0.3
2 +	1.0

Dipstick Result	Amount of Protein in Urine ($g\ L^{-1}$)
3 +	3.0
4 +	10.0
–	–

B) DEGREE OF EDEMA:

Physical Findings	Score
Minimal edema of lower extremities	1
Marked edema of lower extremities	2
Edema of lower extremities, face, hands	3
Generalized massive edema including abdomen and sacrum	4

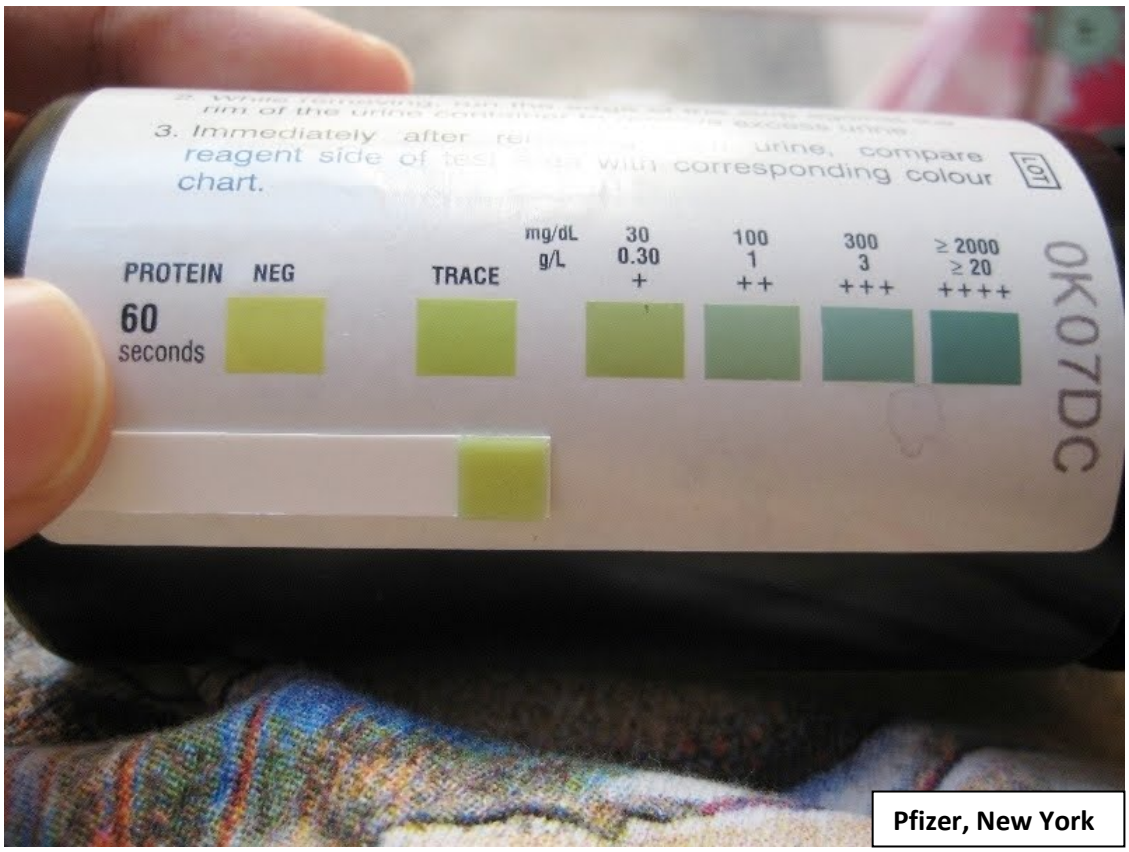
C) DEEP TENDON REFLEX GRADING:

Physical Result	Grade
None elicited	0
Sluggish or dull	1
Active, normal	2
Brisk	3
Brisk with transient (few beats) or sustained (continuous) clonus	4

Appendix-8: Measurement of the Patient's B. P. by the Investigator

Appendix - 9: Examination of the Preeclamptic Patient by the Investigator

Appendix - 10: Dipstick for Proteinuria Measurement



Pfizer, New York

Appendix - 11: Comparison of Mercury and Aneroid Sphygmomanometers

In the study for patients' blood pressure (B.P.) measurements, two high precision sphygmomanometers were employed - *Nova-presameter® mercury sphygmomanometer* (Riester, Jungingen, Germany) and FDA approved SP-110 *Santadical® Aneroid Sphygmomanometer* (SantaMedcal, Los Angeles, USA). The 3M™ Littmann® Master Classic II Stethoscope (New York, USA) was employed to complete B.P. monitoring.

A comparison (n = 82) was made to understand the actual performance of both the sphygmomanometers (Figure 19). For this the same standardized technique (Pickering, 2005; Daskalopoulou, 2012; Hypertension Canada, 2018) was followed and the 'Best Practice Points' recommended for pregnant women (Magee *et al.*, 2016). For the comparison the other variables were kept constants and the same patient was chosen for each B.P. measurement.

Least-square regression analysis yielded $y = 1.075x - 5.224$ ($R^2 = 0.987$). The dashed line indicates a 1:1 correlation. Aneroid measurements yielded slight greater values than those of mercury measurements, especially at higher diastolic blood pressures ($P < 0.001$ by paired t-analysis at 99% CI).

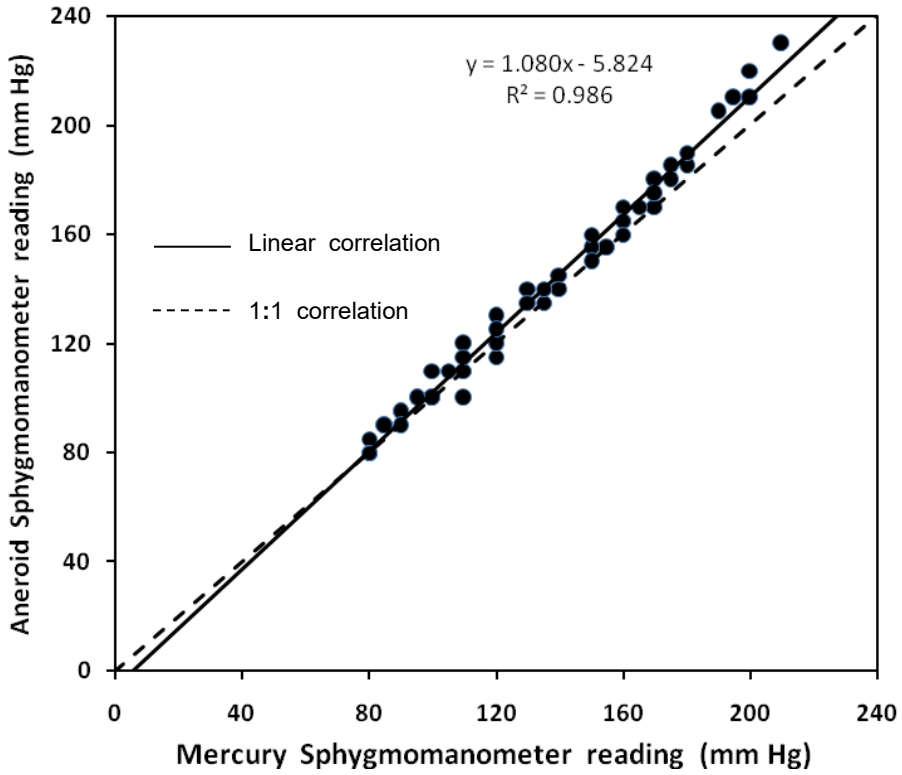


Figure 46. Correlation of B.P. measurements with mercury and aneroid sphygmomanometers**.**

Since the overall correlation between mercury and aneroid sphygmomanometers were roughly 1**:**1, aneroid instrument was utilized for B.P. measurements for most of the hypertensive patients**.** Because the aneroid instrument is easy to carry, smaller in size and free from contamination of mercury vapor (Turner *et al.*, 2007)**.**

The sphygmomanometers utilized in the present investigation to monitor blood pressure of preeclamptic patients were also employed by other authors (Rath and Fischer, 2009; Zibaeenezhad *et al.*, 2010) for estimation of pregnancy induced hypertension**.** They reported the instruments as of Gold Standard**.**